Journal of Fluorine Chemistry 137 (2012) 22–26

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

2-Cyano-6-(trifluoromethyl)-4*H*-pyran-4-one: A novel versatile CF_3-containing building block

Boris I. Usachev [a,*], Dmitrii L. Obydennov [a], Gerd-Volker Röschenthaler [b], Vyacheslav Ya. Sosnovskikh [a]

[a] Department of Chemistry, Ural Federal University, Kuybysheva st., 48, 620026 Ekaterinburg, Russia
[b] School of Engineering and Science, Jacobs University Bremen gGmbH, Campus Ring 1, 28759 Bremen, Germany

ARTICLE INFO

Article history:
Received 21 December 2011
Received in revised form 24 January 2012
Accepted 24 January 2012
Available online 16 February 2012

Keywords:
2-Cyano-6-(trifluoromethyl)-4*H*-pyran-4-one
Carbamoylated aminoenones
Rotamers
Trifluoromethylated 2-pyridones
Oxindole

ABSTRACT

A highly electrophilic pyrone, 2-cyano-6-(trifluoromethyl)-4*H*-pyran-4-one, was synthesized. The reactions of this cyanopyrone with N-nucleophiles can proceed with or without substitution of the cyano group to give a wide range of novel trifluoromethylated compounds. An oxindole derivative was synthesized from a phenylhydrazide using unusual (acidic) conditions.

1. Introduction

Trifluoromethylated and other fluoroalkylated pyrones [1] are still poorly investigated compounds. The pyrone ring activated by the trifluoromethyl group easily reacts with some nucleophilic reagents, resulting in CF_3-bearing heterocycles [1a,c–h,j,m,n]. However, the scope of nucleophiles, which are known to give preparatively useful results in the reactions with CF_3-pyrones, is currently very limited.

2-Cyano-4-pyrones described in the literature [2] can be prepared from the corresponding 4-pyrone-2-carboxamides [2a–d], -carbaldehyde oximes [2e], -carbaldehyde dimethylhydrazones [2f], and from kojic acid derivatives [2g–i]. Chemical properties of 2-cyanopyrones practically were not investigated. It is known that azide anion reacts with 6- [2a–c] and 5-aryl-substituted [2c] 2-cyano-4-pyrones on the cyano group without affecting the pyrone ring to produce 2-tetrazolyl-4-pyrones. Alcoholysis of 2-cyano-5-methoxy-4-pyrone also proceeds at the cyano group to give the corresponding esters [2g]. Reactions of the 2-cyano-4-pyrones with other nucleophiles are unknown so far.

In this paper, we report the synthesis and some properties of 2-cyano-6-(trifluoromethyl)-4-pyrone, the first representative of trifluoromethylated cyano-4-pyrones.

2. Results and discussion

We have shown that dehydration of pyronecarboxamide **1** [1g] with trifluoroacetic anhydride in the presence of pyridine [2a] leads to the formation of 2-cyano-6-(trifluoromethyl)-4-pyrone **2** (through intermediate **A**) in 61% yield (Scheme 1). It was found that pyrone **2** due to the activation of the conjugated system by two electron-withdrawing groups (CF_3 and CN) is a highly electrophilic substrate, which is able to react with different nucleophiles with or without affecting the pyrone ring.

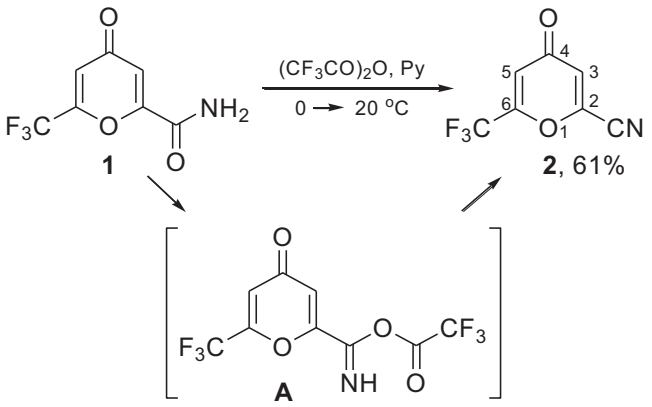
These reactions can be formally separated into two groups: the reactions proceeding with substitution of the cyano group and the reactions proceeding without substitution of the cyano group (Scheme 2).

To the first group belong the reactions of **2** with amines and hydrazines in polar protic solvents, whereas the second group includes the reactions with phenylhydrazine in a nonpolar solvent (toluene) and hydroxylamine. Thus, cyanopyrone **2** easily reacted with both benzylamine and aniline in EtOH at −20 °C to produce carbamoylated aminoenones **3a,b** in 86–78% yield (Scheme 2). This reaction describes a very high reactivity of the pyrone ring of **2** in contrast to the pyrone ring of other 2-cyano-4-pyrones. Isolated products **3** show that the reaction mechanism includes nucleophilic attack by the NH_2 group of an amine at the C-2 and C-6 atoms of **2**.

The regiochemistry of the reactions of **2** with hydrazine and phenylhydrazine in EtOH is similar to those observed in the case of

* Corresponding author.
E-mail address: boris.usachev@mail.ru (B.I. Usachev).

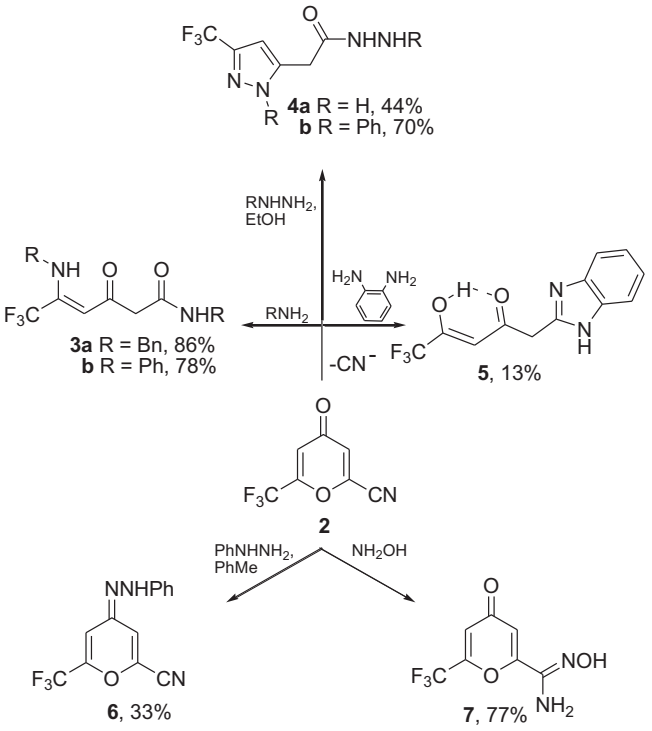
0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2012.01.006



Scheme 1.

the amine attack. These reactions afforded derivatives of 2-(3-(trifluoromethyl)pyrazol-5-yl)acetic acid **4a,b** in 44 and 70% yields, respectively. The interaction of **2** with *o*-phenylenediamine in acetic acid solution at ambient conditions led to the formation of benzimidazole derivative **5** (the double attack of two NH_2 groups at the C-2 carbon), which was isolated from a complex mixture of other products in 13% yield.

It was found that phenylhydrazine attacks pyrone **2** in a non-polar medium at the atom C-4, and this result is in agreement with our previous findings on a strong solvent influence on the reaction route by using pyrones related to **2** as substrates [1f]. Heating **2** with this nucleophile in toluene resulted in the formation of phenylhydrazone **6**, but the yield of this compound did not exceed 33% because resinification. The difference in the regioselectivity of nucleophilic attack can be explained by the effective stabilization of highly polar cyclic tetrahedral addition intermediates (attack at the C-2 carbon of the pyrone ring) in polar solvents, which cannot be easily formed in nonpolar media. Surprisingly, the reaction between **2** and hydroxylamine in ethanol proceeds by the nucleophilic addition to the cyano group to give amidoxime **7** in 77% yield (Scheme 2). This reaction path can be explained by hardness of hydroxylamine, which is a harder base then hydrazines, and reacts with a harder acid then the C-2 atom, the carbon of the cyano group. The structures of compounds **3–7** were confirmed from NMR, IR spectra and elemental analysis. In the ^{1}H NMR spectra of carbamoylated aminoenones **3**, the characteristic singlets due to the methylene (δ 3.36 (**3a**); 3.64 (**3b**)) and vinyl (δ 5.75 (**3a**); 6.04 (**3b**)) protons were observed. The amide and enamine NH protons in **3a** appeared as triplets at δ 8.57 ($^3J_{NH,CH_2}$ = 5.9 Hz) and 10.25 ($^3J_{NH,CH_2}$ = 6.7 Hz), whereas the same protons in **3b** appeared as singlets at δ 10.16 and 11.26, respectively.



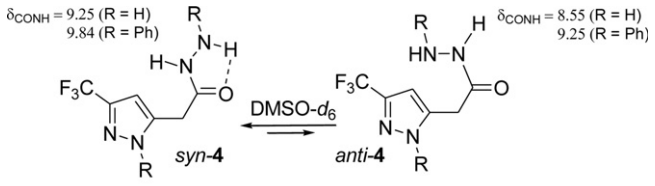
Scheme 2.

In the ^{1}H NMR spectra (DMSO-d_6) of hydrazides **4**, two sets of signals belonging to *syn*-**4** and *anti*-**4** rotamers [3] were observed (Scheme 3). The corresponding protons (besides the PhNH protons) in the corresponding *sin*- and *anti*-rotamers have almost the same chemical shifts. Intramolecular hydrogen bond-stabilized *syn*-**4a,b** rotamers (major) can be recognized in the ^{1}H NMR spectra by the low-field signals of the CONH protons, which appeared at δ 9.25 (*syn*-**4a**) and 9.84 (*syn*-**4b**), whereas the same protons in the minor (*anti*-) rotamers appeared as signals at the higher field (δ 8.55 and 9.25, respectively). According to the spectral data the equilibria molar ratios of *syn*-**4** to *anti*-**4** in DMSO-d_6 are 95:5 (**4a**) and 84:16 (**4b**) (Scheme 3).

In the ^{19}F NMR spectrum (DMSO-d_6, C_6F_6) of **4a** two singlets due to the CF_3 groups in *syn*- (δ 102.3) and *anti*- (δ 102.4) rotamers were observed. The corresponding singlets at δ 101.8 and 101.9 were found in the ^{19}F NMR spectrum of **4b**. The ^{19}F NMR spectroscopy confirms the ratios of the rotamers as stated above. The regioisomeric 3-CF_3-pyrazolic structure of **4b** was confirmed by the synthesis of the parent carboxylic acid (see below).

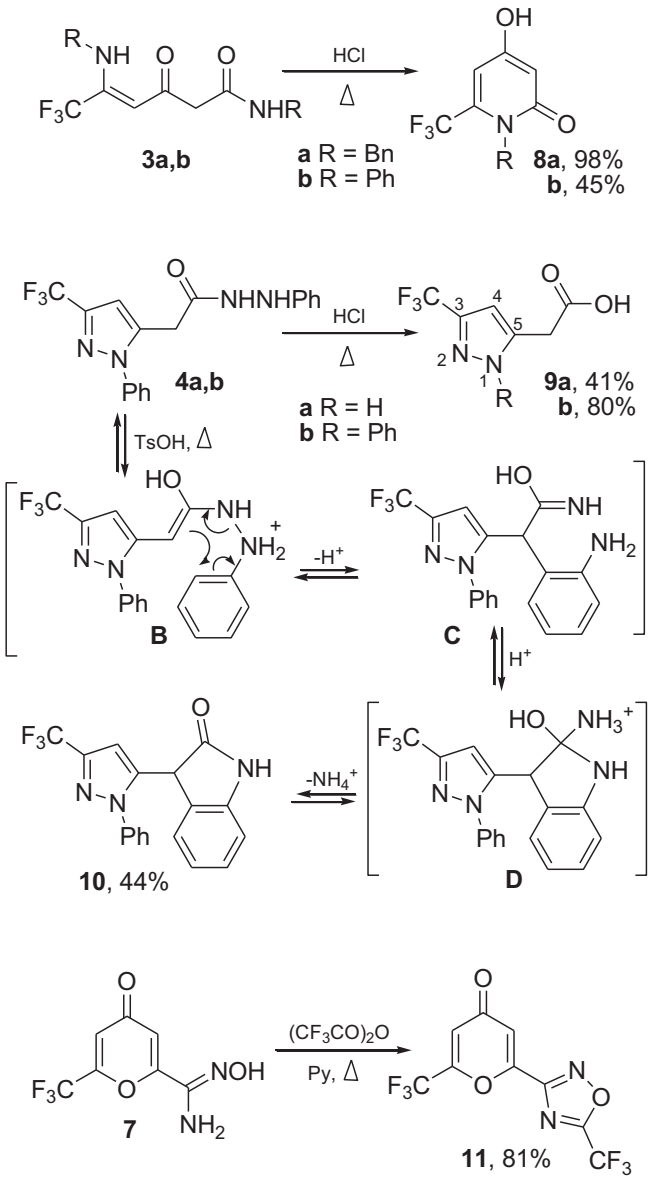
In the ^{1}H NMR spectrum of benzimidazole derivative **5** besides the signals of the aromatic protons, singlets due to the methylene (δ 3.42) and vinyl (δ 5.81) protons were observed. Two labile protons appeared as singlets at δ 10.63 and 12.33. In the ^{19}F NMR spectrum (DMSO-d_6, C_6F_6) of **5** a high-field singlet at δ 87.0 due to the CF_3 group was observed, thus additionally confirming the enolized diketone structure. In the ^{1}H NMR spectra of compounds **6** and **7**, the protons H-3 and H-5 appeared as characteristic doublets in the range of δ 6.8–7.7 (^4J = 2.2 Hz), proving their pyrone nature [1g].

Derivatives synthesized from 2-cyano-6-(trifluoromethyl)-4-pyrone **2** can be used in subsequent transformations for the preparation of novel trifluoromethylated building blocks. Thus, treatment of carbamoylated aminoenones **3a,b** with HCl in THF, led to the formation of 4-hydroxy-6-(trifluoromethyl)-2-pyridones **8a,b**, the first representatives of trifluoromethylated 3,5-unsubstituted 4-hydroxy-2-pyridones, in 98 and 45% yields, respectively (Scheme 4).



	syn-**4** (%)	*anti*-**4** (%)
a (R = H)	95	5
b (R = Ph)	84	16

Scheme 3.



Scheme 4.

Hydrolysis of the hydrazides **4a,b** in the presence of HCl resulted in the formation of 2-[3-(trifluoromethyl)pyrazol-5-yl]acetic (**9a**, 41%) and 2-[1-phenyl-3-(trifluoromethyl)pyrazol-5-yl]acetic (**9b**, 80%) acids, which were prepared for the first time. The regioisomeric 3-CF_3-pyrazolic structure of **9b** was confirmed by the ^{13}C NMR spectroscopy. In the ^{13}C NMR spectrum of **9b**, a low-field quartet due to the most deshielded pyrazole carbon C-3 at δ 141.0 ($^2J_{C,F}$ = 37.5 Hz) was observed, confirming this regiochemistry.

It is known, that oxindole derivatives can be synthesized through deprotonation of some phenylhydrazides with strong bases (Brunner reaction, an analog to the Fischer indole synthesis) [4a,b] as well as via alkylidenation of *N*,*N*′-dimethylated phenylhydrazides using phosphoranes [4c]. There are no data on the use of acidic conditions (conditions of the Fischer reaction) for the formation of the indole ring via cyclization of phenylhydrazides. We have found that phenylhydrazide **4b** undergoes transformation into indole **10** (44%) by heating in toluene in the presence of TsOH within 4 h (Scheme 4). This reaction is the first example of indole synthesis from a phenylhydrazide in the conditions of the Fischer reaction. The formation of the oxindole in acidic conditions can be explained by relatively high stability of the main intermediate **B** due to its push-pull electronic structure (Scheme 4). The structure of oxindole **10** was confirmed from ^1H NMR, IR spectroscopies, and elemental analysis. In the ^1H NMR spectrum of **10** besides signals due to nine protons of the benzene rings, singlets due to the methine (δ 5.11), pyrazole (δ 6.66), and NH (δ 10.64) protons were observed.

Heating amidoxime **7** with trifluoroacetic anhydride in the presence of pyridine gave 2-(trifluoromethyl)-6-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-4-pyrone **11** in 81% yield. Pyrone **11** was characterized by conventional spectroscopic methods.

3. Conclusion

Thus, we have synthesized the first representative of trifluoromethylated cyano-4-pyrones, 2-cyano-6-(trifluoromethyl)-4-pyrone, shown its high reactivity towards *N*-nucleophiles and revealed its rich chemistry. It was found that this highly electrophilic pyrone can be used as a novel CF_3-containing building block for the regioselective syntheses of various trifluoromethylated heterocycles. These results will be very useful for development of chemistry of other functionalized $CF_3(R^F)$-bearing cyano-4-pyrones and related compounds.

4. Experimental

4.1. General

^1H, ^{19}F and ^{13}C NMR spectra were recorded on Bruker AVANCE DRX-400 spectrometer. Chemical shifts for ^1H NMR spectra are reported in parts per million (ppm) downfield from TMS. ^{19}F NMR spectra were externally referenced against C_6F_6 (δ = −163 relative to $CFCl_3$). Coupling constants (*J*) are given in hertz (Hz). Infrared spectra (IR) were recorded on Nicolet 6700 spectrometer, equipped with attenuated total reflection accessory (ATR), absorbance frequencies are given at maximum of intensity in cm^{-1}.

4.2. 2-Cyano-6-(trifluoromethyl)-4H-pyran-4-one (2)

4-Oxo-6-(trifluoromethyl)-4*H*-pyran-2-carboxamide [1g] **1** (8.0 g, 38.6 mmol) was added to a mixture of dioxane (75 mL) and pyridine (7.8 mL). To the mixture cooled in an ice bath was gradually added with stirring trifluoroacetic anhydride (9.7 mL). The mixture was stirred for 5 min on ice and then 30 min at ambient conditions. The resulting solution was diluted with water (100 mL) and the product was extracted twice with chloroform (50 mL portions). In distillation, the main fraction was collected at 98–102 °C/~25 Torr to give compound **2** as a colourless liquid (4.45 g, 61%); ν_{max} (ATR) 2340, 1673, 1407, and 1349 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.84 (1H, d, *J* 2.0 Hz, H-5), 6.91 (1H, d, *J* 2.0 Hz, H-3); δ_H (400 MHz, DMSO-d_6) 6.71 (1H, d, *J* 2.5 Hz, H-5), 6.92 (1H, d, *J* 2.5 Hz, H-3); δ_F (376.5 MHz, $CDCl_3$, C_6F_6) 90.3 (s, CF_3); [found: C, 44.39; H, 0.87; N, 7.71. $C_6H_2F_3NO_2$ requires C, 44.46; H, 1.07; N, 7.41%].

4.3. (Z)-N-benzyl-5-(benzylamino)-6,6,6-trifluoro-3-oxohex-4-enamide (3a)

A cooled to −20 °C solution of benzylamine (0.85 g, 7.8 mmol) in ethanol (2 mL) was added to a cooled to −20 °C solution of **2** (0.50 g, 2.6 mmol) in ethanol (2 mL). The mixture was kept at −20 °C for 2 d. The residue was filtered off, washed with cold ethanol and the filtrate was diluted with water (5 mL). The residue from the filtrate was filtered off, washed with water and dried. The combined residue was crystallized from a mixture of hexane (25 mL) and toluene (7 mL) to give compound **3a** (0.84 g, 86%) as

yellow crystals, mp 98 °C; ν_{max} (ATR) 3279, 1644, 1601, 1545, and 1496 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.36 (2H, s, CH_2), 4.28 (2H, d, J 5.9 Hz, CH_2), 4.55 (2H, d, J 6.7 Hz, CH_2), 5.75 (1H, s, =CH), 7.22–7.41 (10H, m, Ph), 8.57 (1H, t, J 5.9 Hz, CONH), 10.25 (1H, t, J 6.7 Hz, NH); [found: C, 63.89; H, 4.88; N, 7.61. $C_{20}H_{19}F_3N_2O_2$ requires C, 63.82; H, 5.09; N, 7.44%].

4.4. (Z)-N-phenyl-5-(phenylamino)-6,6,6-trifluoro-3-oxohex-4-enamide (3b)

A cooled to −20 °C solution of aniline (0.74 g, 7.8 mmol) in ethanol (2 mL) was added to a cooled to −20 °C solution of **2** (0.50 g, 2.6 mmol) in ethanol (2 mL). The reaction mixture was kept at −20 °C for 2 d. The residue was filtered off, washed with cold ethanol and the filtrate was diluted with water (5 mL). The residue from the filtrate was filtered off, washed with water (2 mL) and dried. The combined residue was crystallized from a mixture of hexane (25 mL) and toluene (5 mL) to give compound **3b** (0.71 g, 78%) as yellow crystals, mp 108 °C; ν_{max} (ATR) 1689, 1659, 1626, 1596, 1578, and 1548 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.64 (2H, s, CH_2), 6.04 (1H, s, =CH), 7.06 (1H, t, J 7.4 Hz, Ph), 7.20–7.44 (5H, m, Ph), 7.59 (2H, dd, J 8.6, 1.0 Hz, Ph), 10.16 (1H, s, CONH), 11.26 (1H, s, NH). δ_F (376.5 MHz, $CDCl_3$, C_6F_6) 100.1 (s, CF_3); [found: C, 62.08; H, 4.13; N, 8.09. $C_{18}H_{15}F_3N_2O_2$ requires C, 62.07; H, 4.34; N, 8.04%].

4.5. 2-[3-(Trifluoromethyl)pyrazol-5-yl]acetohydrazide (4a)

A cooled solution of pyrone **2** (0.20 g, 1.1 mmol) in ethanol (1 mL) was added to a cooled solution of hydrazine hydrate (3 drops) in ethanol (1 mL). The reaction mixture was stirred at 0 °C for 1 h. The residue was filtered off, washed with ethanol (1 mL) and dried to give compound **4a** (0.097 g, 44%) as colourless crystals, mp 184–185 °C; ν_{max} (ATR) 3298, 3238, 3184, 1644, 1544, and 1499 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.49 (2H, s, CH_2), 4.26 (2H, s, NH_2), 6.48 (1H, s, CH-pyraz.), 9.25 (1H, s, CONH), 13.1–13.7 (1H, br s, NH-pyraz.); δ_F (376.5 MHz, DMSO-d_6, C_6F_6) 102.3 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 30.5 (CH_2), 102.7 (C4), 121.9 (q, $^1J_{C,F}$ 267.9 Hz, CF_3), 139.2 (C5), 140.9 (q, $^2J_{C,F}$ 36.7 Hz, C3), 167.1 (CO); [found: C, 34.58; H, 3.38; N, 26.85. $C_6H_7F_3N_4O$ requires C, 34.62; H, 3.39; N, 26.92%].

4.6. N′-phenyl-2-[N-phenyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]acetohydrazide (4b)

A cooled to −20 °C solution of pyrone **2** (1.0 g, 5.3 mmol) in ethanol (5 mL) was added to a cooled to −20 °C solution of phenylhydrazine (1.25 g, 11.6 mmol) in ethanol (5 mL). The reaction mixture was kept at −5 °C conditions for 2 d. Then the reaction mixture was diluted with water (50 mL), the resulting residue was filtered off, washed with water (5 mL), dried and crystallized from toluene to give compound **4b** (1.33 g, 70%) as a white solid, mp 151–152 °C; δ_H (400 MHz, DMSO-d_6): *syn*-**4b** (84%) 3.78 (2H, s, CH_2), 6.55 (2H, d, J 7.6 Hz, Ph), 6.69 (1H, t, J 7.3 Hz, Ph), 6.88 (1H, s, pyraz.), 7.10 (2H, t, J 7.5 Hz, Ph), 7.56–7.62 (5 H, m, Ph), 7.73 (1H, d, J 2.4 Hz, PhN<u>H</u>NH), 9.84 (1H, d, J 2.4 Hz, PhNHN<u>H</u>), *anti*-**4b** (16%) 3.79 (2H, s, CH_2), 6.56 (2H, d, Ph), 6.76 (1H, t, J 7.3 Hz, Ph), 6.83 (1H, s, pyraz.), 7.14 (2H, t, J 7.5 Hz, Ph), 7.43–7.47 (2H, m, Ph), 7.51–7.55 (3H, m, Ph), 7.95 (1H, s, PhN<u>H</u>NH), 9.25 (1H, s, PhNHN<u>H</u>); δ_F (376.5 MHz, DMSO-d_6, C_6F_6) *syn*-**4b** (84%) 101.8 (s, CF_3); *anti*-**4b** (16%) 101.9 (s, CF_3); [found: C, 59.70; H, 4.08; N, 15.38. $C_{18}H_{15}F_3N_4O$ requires C, 60.00; H, 4.20; N, 15.55].

4.7. (Z)-1-(1H-Benzo[d]imidazol-2-yl)-5,5,5-trifluoro-4-hydroxypent-3-en-2-one (5)

To a solution of pyrone **2** (0.20 g, 1.1 mmol) in acetic acid (2 mL) was added *o*-phenylenediamine (0.12 g, 1.2 mmol). The reaction mixture was kept at ambient conditions for 7 d, and then diluted with water (10 mL) with conc. HCl (3 drops). The resulting residue was filtered off, crystallized from ethanol (5 mL), washed with ethanol (1 mL) and dried to give compound **5** (44 mg, 13%) as an orange solid, mp 254–256 °C (decomp.); ν_{max} (ATR) 1681, 1597, 1574, 1524 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.42 (2H, s, CH_2), 5.81 (1H, s, =CH), 7.17–7.27 (m, 2 H, arom.); 7.33 (td, J = 7.6, 1.3 Hz, 1 H, arom.); 7.49 (1H, dd, J 8.0, 1.0 Hz, arom.), 10.63 (1H, s, NH), 12.33 (1H, s, OH); δF (376.5 MHz, DMSO-d_6, C_6F_6) 87.0 (s, CF_3); [found: C, 48.51; H, 3.59; N, 9.35. $C_{12}H_9F_3N_2O_2 \cdot 1.5\ H_2O$ requires C, 48.49; H, 4.07; N, 9.42%].

4.8. 2-Cyano-6-(trifluoromethyl)-4H-pyran-4-one phenylhydrazone (6)

Phenylhydrazine (0.16 g, 1.5 mmol) was added to a solution of pyrone **2** (0.25 g, 1.3 mmol) in toluene (2 mL). The reaction mixture was refluxed for 2 h and then cooled to ambient temperature. The resulting residue was filtered off and recrystallized from toluene to give compound **6** (0.12 g, 33%) as a red solid, mp 214–215 °C; δ_H (400 MHz, DMSO-d_6): 6.80 (1H, d, J 2.2 Hz, H-5), 6.82 (1H, t, J 7.3 Hz, Ph), 7.10 (2H, d, J 7.7 Hz, Ph), 7.23 (2H, t, J 7.5 Hz, Ph), 7.69 (1H, d, J 2.2 Hz, H-3); δ_F (376.5 MHz, DMSO-d_6, C_6F_6) 92.0 (s, CF_3); [found: C, 55.79; H, 2.81; N, 14.99. $C_{13}H_8F_3N_3O$ requires C, 55.92; H, 2.89; N, 15.05%].

4.9. 4-Oxo-6-(trifluoromethyl)-4H-pyran-2-amidoxime (7)

A solution of hydroxylamine prepared in ethanol (2 mL) from $NH_2OH \cdot HCl$ (0.36 g, 5.6 mmol) and KOH (0.23 g, 5.3 mmol) was added to a cooled solution of pyrone **2** (0.50 g, 2.65 mmol) in ethanol (2 mL). The reaction mixture was stirred at 0 °C for 30 min. The residue was filtered off, crystallized from ethanol (25 mL) and dried to give compound **7** (0.45 g, 77%) as a white solid, mp ~237 °C (subl.); ν_{max} (ATR) 3290, 1640 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 6.10 (2H, s, NH_2), 6.86 (1H, d, J 2.2 Hz, H-5), 7.04 (1H, d, J 2.2 Hz, H-3), 10.73 (1H, s, OH); δ_F (376.5 MHz, DMSO-d_6, C_6F_6) 92.4 (s, CF_3); [found: C, 37.81; H, 2.46; N, 12.52. $C_7H_5F_3N_2O_3$ requires C, 37.85; H, 2.27; N, 12.61].

4.10. N-benzyl-4-hydroxy-6-(trifluoromethyl)-2-pyridone (8a)

To a solution of enaminone **3a** (0.10 g, 0.27 mmol) in ethanol (2 mL) was added conc. HCl (0.5 mL). The mixture was kept for 3 weeks at ambient temperature. The reaction mixture was diluted with water (10 mL), the resulting residue was crystallized from a mixture of petroleum ether and toluene (4:1, 10 mL) to give compound **8a** (70 mg, 98%) as beige solid, mp 166–167 °C. Alternatively, compound **8a** was prepared by treatment of a solution of enaminone **3a** (0.11 g, 0.29 mmol) in THF (2 mL) with conc. HCl (0.5 mL). The mixture was refluxed for 6 h and then diluted with water (10 mL) to give compound **8a** in 47% yield, mp 166–167 °C (toluene); ν_{max} (ATR) 3093, 1658, 1630, 1560, 1496 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.18 (2H, s, CH_2), 5.95 (1H, d, J 2.4 Hz, H-3), 6.57 (1H, d, J 2.4 Hz, H-5), 7.01 (2H, d, J 7.3 Hz, Ph), 7.22 (1H, t, J 7.3 Hz, Ph), 7.30 (2H, t, J 7.3 Hz, Ph), 10.9–11.9 (1H, br s, OH); [found: C, 58.01; H, 3.97; N, 5.22. $C_{13}H_8F_3N_3O$ requires C, 58.00; H, 3.74; N, 5.22%].

4.11. N-phenyl-4-hydroxy-6-(trifluoromethyl)-2-pyridone (8b)

To a solution of enaminone **3b** (0.10 g, 0.29 mmol) in THF (2 mL) was added conc. HCl (0.5 mL). The mixture was refluxed for 6 h and then diluted with water (10 mL). The resulting residue was crystallized from toluene (2 mL) to give compound **8b** (33 mg, 45%) as beige solid, mp 208–209 °C; δ_H (400 MHz, DMSO-d_6) 5.89 (1H, d,

J 2.2 Hz, H-3), 6.55 (1H, d, *J* 2.2 Hz, H-5), 7.22–7.32 (2H, m, Ph), 7.43–7.53 (3H, m, Ph), 11.42 (1H, br s, OH); [found: C, 56.17; H, 3.16; N, 5.56. $C_{12}H_8F_3NO_2$ requires C, 56.48; H, 3.16; N, 5.49%].

4.12. 2-[3-(Trifluoromethyl)pyrazol-5-yl]acetic acid (9a)

Hydrazide **4a** (0.24 g, 1.15 mmol) was refluxed in conc. HCl (2 mL) for 4 h. After cooling the reaction mixture to −20 °C, the residue (N_2H_4·2 HCl) was filtered off, the filtrate was collected, water and HCl were evaporated the filtrate and the residue was crystallized from a mixture of petroleum ether and toluene to give compound **9a** (91 mg, 41%) as a white solid, mp 140–141 °C; δ_H (400 MHz, DMSO-d_6) 3.7 (2H, s, CH_2), 6.55 (1H, s, pyraz.), 12.5–12.9 (1H, br s, NH), 13.45 (1H, br s, CO_2H); [found: C, 37.16; H, 2.65; N, 14.45. $C_6H_5F_3N_2O_2$ requires C, 37.13; H, 2.50; N, 14.43].

4.13. 2-[N-phenyl-3-(trifluoromethyl)pyrazol-5-yl]acetic acid (9b)

Phenylhydrazide **4b** (0.20 g, 0.60 mmol) was added to conc. HCl (7 mL). The reaction mixture was refluxed for 6 h, cooled to ambient temperature, and then diluted with water (8 mL). The resulting residue was filtered off and crystallized from a mixture of petroleum ether and toluene (1:1, 5 mL) to give compound **9b** (0.12 g, 80%) as colourless crystals, mp 125–126 °C; ν_{max} (ATR) 3140, 1702, 1597, 1502, 1484 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 3.84 (2H, s, CH_2), 6.89 (1H, s, pyraz.), 7.46–7.61 (5H, m, Ph), 12.5–13.0 (1H, br s, CO_2H); δ_F (376.5 MHz, DMSO-d_6, C_6F_6) 101.9 (s, CF_3); δ_C (100 MHz, DMSO-d_6) 31.6 (CH_2), 106.2 (buried q, C4), 121.5 (q, $^1J_{C,F}$ = 268.4 Hz, CF_3), 125.3 (Ph), 129.2 (Ph), 129.5 (Ph), 138.3 (Ph), 139.4 (C5), 141.0 (q, $^2J_{C,F}$ = 37.5 Hz, C3), 169.9 (CO); [found: C, 53.45; H, 3.19; N, 10.32. $C_{12}H_9F_3N_2O_2$ requires C, 53.34; H, 3.36; N, 10.37%].

4.14. 3-[1-Phenyl-3-(trifluoromethyl)pyrazol-5-yl]indolin-2-one (10)

A mixture of phenylhydrazide (0.20 g, 0.55 mmol) and TsOH (0.28 g) was refluxed in toluene for 4 h. The hot solution was passed through silica gel (1 cm^3), and the solvent from filtrate was evaporated. The residue was crystallized from aqueous ethanol to give compound **10** (0.083 g, 44%) as a white solid, mp 200–202 °C; ν_{max} (ATR) 3084, 1705, 1621, 1483; δ_H (400 MHz, DMSO-d_6) 5.11 (1H, s, CH), 6.66 (1H, s, pyraz.), 6.80 (1 H, d, *J* 7.8 Hz, arom.), 6.94 (1H, t, *J* 7.5 Hz, arom.), 7.08 (1H, d, *J* 7.5 Hz, arom.), 7.21 (1H, t, *J* 7.8 Hz, arom.), 7.45–7.55 (5H, m, Ph), 10.64 (1H, s, NH); [found: C, 62.91; H, 3.64; N, 12.17. $C_{18}H_{12}F_3N_3O$ requires C, 62.97; H, 3.52; N, 12.24%].

4.15. 2-(Trifluoromethyl)-6-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-4-pyrone (11)

Trifluoroacetic anhydride (0.57 g, 2.7 mmol) was added to a mixture of amidoxime **7** (0.20 g, 0.90 mmol), CH_2Cl_2 (4 mL) and pyridine (0.21 g). The mixture was refluxed for 1 h, then cooled to ambient temperature, CH_2Cl_2 distilled off under reduced pressure, and the residue quenched with water (5 mL). The resulting residue was crystallized from petroleum ether to give compound **11** (0.22 g, 81%) as colourless crystals, mp 87–88 °C; δ_H (400 MHz, DMSO-d_6) 7.26 (1H, d, *J* 2.0 Hz), 7.30 (1H, d, *J* 2.0 Hz); δ_F (376.5 MHz, DMSO-d_6, C_6F_6) 92.5 (3F, s, pyrone-CF_3); 98.0 (3F, s, oxadiaz.-CF_3); [found: C, 36.04; H, 0.67; N, 9.35. $C_9H_2F_6N_2O_3$ requires C, 36.02; H, 0.67; N, 9.33%].

Acknowledgments

The authors thank Ural Federal University and the Deutsche Forschungsgemeinschaft for financial support (grant No. RO 362/45-1).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2012.01.006.

References

[1] (a) V.I. Tyvorskii, D.N. Bobrov, Chem. Heterocycl. Compd. 33 (1997) 995–996;
(b) V.I. Tyvorskii, D.N. Bobrov, O.G. Kulinkovich, N.D. Kimpe, K.A. Tehrani, Tetrahedron 54 (1998) 2819–2826;
(c) V.I. Tyvorskii, D.N. Bobrov, Chem. Heterocycl. Compd. 34 (1998) 679–682;
(d) V.I. Tyvorskii, D.N. Bobrov, O.G. Kulinkovich, K.A. Tehrani, N. De Kimpe, Tetrahedron 57 (2001) 2051–2055;
(e) V.I. Tyvorskii, D.N. Bobrov, O.G. Kulinkovich, W. Aelterman, N. De Kimpe, Tetrahedron 56 (2000) 7313–7318;
(f) B.I. Usachev, D.L. Obydennov, V.Y. Sosnovskikh, M.I. Kodess, Tetrahedron Lett. 50 (2009) 4446–4448;
(g) B.I. Usachev, I.A. Bizenkov, V.Y. Sosnovskikh, Russ. Chem. Bull. 56 (2007) 558–559;
(h) S. Babu, M.J. Pozzo, J. Heterocycl. Chem. 28 (1991) 819–821;
(i) R.N. Serdyuk, A.Y. Sizov, A.F. Ermolov, Russ. Chem. Bull. 52 (2003) 1854–1858;
(j) C.L. Yeates, J.F. Batchelor, E.C. Capon, N.J. Cheesman, M. Fry, A.T. Hudson, M. Pudney, H. Trimming, J. Woolven, J.M. Bueno, J. Chicharro, E. Fernández, J.M. Fiandor, D. Gargallo-Viola, F.G. Heras, E. Herreros, M.L. León, J. Med. Chem. 51 (2008) 2845–2852;
(k) J. Boivin, L. El Kaim, S.Z. Zard, Tetrahedron 51 (1995) 2585–2592;
(l) A. Bunescu, S. Reimann, M. Lubbe, P. Langer, A. Spannenberg, J. Org. Chem. 74 (2009) 5002–5010;
(m) V.Y. Sosnovskikh, V.Y. Korotaev, D.L. Chizhov, I.B. Kutyashev, D.S. Yachevskii, O.N. Kazheva, O.A. Dyachenko, V.N. Charushin, J. Org. Chem. 71 (2006) 4538–4543;
(n) D.S. Yachevskii, D.L. Chizhov, V.N. Charushin, Russ. J. Org. Chem. 42 (2006) 142–144;
(o) D.C. England, J. Org. Chem. 46 (1981) 147–153.

[2] (a) Y. Honma, Y. Sekine, T. Hashiyama, M. Takeda, Y. Ono, K. Tsuzurahara, Chem. Pharm. Bull. 30 (1982) 4314–4324;
(b) A. Shahrisa, S. Hemmati, Indian J. Chem., Sect. B 39 (2000) 190;
(c) B.P. Clark, W.J. Ross, A. Todd, U.S. Patent 4,304,728 (1981).;
(d) B.P. Clark, W.J. Ross, A. Todd, U.S. Patent 4,364,956 (1982).
(e) G.A. Poulton, M.E. Williams, J. Heterocycl. Chem. 12 (1975) 219–220;
(f) J. Mlochowski, M. Giurg, M. Uher, A. Korenova, D. Vegh, J. Prakt. Chem. 338 (1996) 65–68;
(g) D.L. McGillivray, G.A. Poulton, J. Mass Spectrom. 15 (1980) 31–34;
(h) M. Iguchi, A. Nishiyama, H. Eto, S. Yamamura, Chem. Lett. (1980) 1323–1326;
(i) A. Nishiyama, H. Eto, M. Iguchi, S. Yamamura, Chem. Pharm. Bull. 31 (1983) 2853–2858.

[3] (a) P. Marakos, N. Pouli, S. Papakonstantinou-Garoufalias, E. Mikros, J. Mol. Struct. 650 (2003) 213–221;
(b) U. Himmelreich, F. Tschwatschal, R. Borsdorf, Monatsh. Chem. 124 (1993) 1041–1051.

[4] (a) R.J. Sundberg, The Chemistry of Indoles, Academic Press, N.Y., London, 1970, p. 362;
(b) J. Wolff, M. Taddei, Tetrahedron 42 (1986) 4267–4272;
(c) K. Hisler, A.G.J. Commeureuc, S. Zhou, J.A. Murphy, Tetrahedron Lett. 50 (2009) 3290–3293.