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Regioselective solvent-sensitive reactions of 6-(trifluoromethyl)comanic acid and its derivatives with phenylhydrazine

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ABSTRACT

6-(Trifluoromethyl)comanic acid reacts regioselectively with phenylhydrazine in water to give 5-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-3-carboxylic acid. Similar reaction in dioxane leads to 3-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-5-carboxylic acid. A strong solvent influence on the reaction route was also found for 6-(trifluoromethyl)comanic acid derivatives.

We recently described a convenient synthesis of 6-(trifluoromethyl)comanic acid [6-(trifluoromethyl)-4-oxo-4*H*-pyran-2-carboxylic acid], its ethyl ester and amide.[1] These cyclic conjugated enones, due to the presence of several reactive positions towards nucleophilic attack, represent very useful CF_3-containing building blocks in organic synthesis.

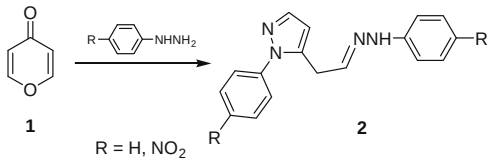
It is known[2] that unsubstituted γ-pyrone **1** reacts with phenylhydrazine and *p*-nitrophenylhydrazine to give pyrazoles **2** (Scheme 1). Earlier investigators[3] have described a number of reactions of various γ-pyrone derivatives with hydrazines, however, the structures of the products have generally not been deduced correctly.

In this Letter, we describe the regioselective reactions of 6-(trifluoromethyl)comanic acid, its ethyl ester, amide and sodium salt with phenylhydrazine under various conditions.

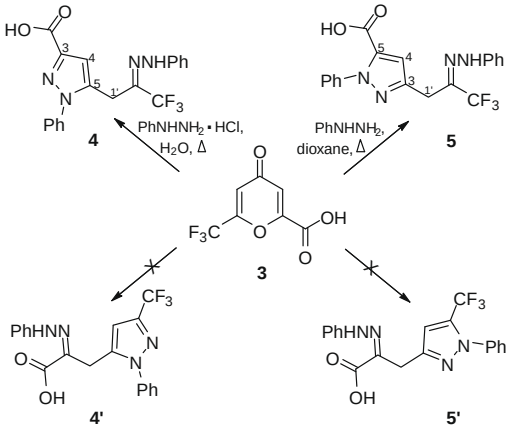
We discovered that these reactions were selective based on the nature of the solvent. Thus, heating 6-(trifluoromethyl)comanic acid **3** with 2.2 equiv of phenylhydrazine hydrochloride in water gave 5-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-3-carboxylic acid **4** in 64% yield. The same reactants in the polar aprotic solvent dioxane led to the formation of the isomeric structure, 3-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-5-carboxylic acid **5**, in 30% yield (Scheme 2). The ^{1}H NMR spectrum of the crude product did not show any signals due to regioisomer **4**.

Heating **3** with phenylhydrazine in non-polar toluene provided a mixture of isomeric pyrazoles **4** and **5** (ratio 1:2), which was characterized by ^{1}H NMR and elemental analysis. This solvent-dependent reaction is important in γ-pyrone chemistry, because it allows the regioselective syntheses of isomeric pyrazoles.

The structures of the pyrazoles **4** and **5** were confirmed from ^{1}H, ^{13}C and ^{19}F NMR spectra using 2D ^{1}H–^{13}C HSQC and HMBC experiments, IR spectra and elemental analysis. Theoretically, the reaction of **3** with phenylhydrazine could provide four isomeric



Scheme 1.



Scheme 2.

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pyrazoles: **4**, **5**, **4́** and **5́** (Scheme 2). However, in the ^{13}C NMR spectra of the products synthesized in water and dioxane, the characteristic quartets due to the C=N hydrazonic carbon atoms at about δ 127 ($^2J_{C,F} \sim 33$ Hz) were observed thus excluding structures **4́** and **5́**. The product prepared in water was characterized as pyrazole **4** (a derivative of pyrazole-3-carboxylic acid). In its ^1H-coupled ^{13}C NMR spectrum, carbon C-3 (the most deshielded carbon of the pyrazole ring) appeared as a doublet at δ 144.5 ($^2J_{C3,H4} = 3.7$ Hz). The ^{13}C NMR spectrum also showed a doublet of triplets at δ 137.8 ($^2J_{C5,H4} = 8.6$ Hz, $^2J_{C5,H1'} = 7.9$ Hz), which corresponds to carbon C-5 (correlations with the signals at δ 6.46 (H-4) and δ 4.05 were observed). The spin–spin couplings were confirmed by ^1H–^{13}C HMBC experiments. The structure of pyrazole **5** (a derivative of pyrazole-5-carboxylic acid), prepared in dioxane, was proved using a similar approach. In the ^1H-coupled ^{13}C NMR spectrum, the most deshielded (by the C=N moiety) carbon C-3 appeared as a multiplet at δ 146.2, whereas carbon C-5 appeared as a doublet at δ 134.9 ($^2J_{C5,H4} = 7.7$ Hz). Characteristic cross-peaks in the ^1H–^{13}C HMBC spectrum were observed between the methylene protons and carbons C-3, C=N (phenylhydrazonic moiety), CF_3 and C-4.

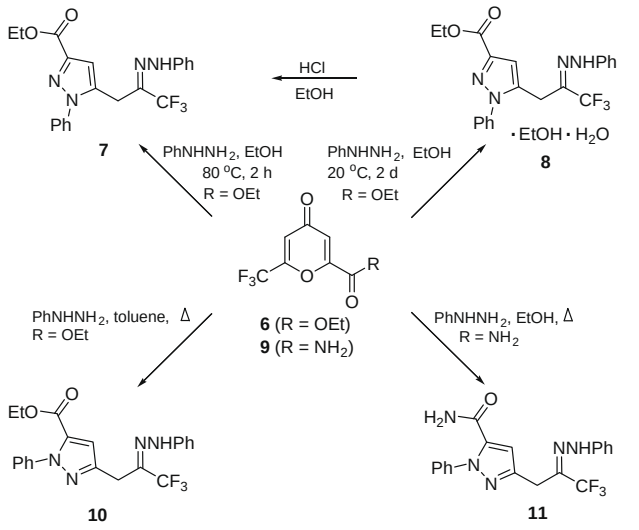
Ethyl 6-(trifluoromethyl)comanoate **6** was reacted with 2.2 equiv of phenylhydrazine in protic polar ethanol (**6** is insoluble in water) to give, as expected, ethyl 5-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-3-carboxylate **7**. Keeping the reaction mixture at room temperature for two days allowed preparation of **7** as a crystalline ethanolate-hydrate solvate **8** (69%, mp 106 °C) which can be transformed into unsolvated pyrazole **7** (mp 199–200 °C) by adding a catalytic amount of HCl or another acid to an ethanolic solution of **8**. Unsolvated pyrazole **7** can also be synthesized rapidly by heating the reaction mixture for 2 h (Scheme 3). On the other hand, the reaction of **6** with phenylhydrazine in refluxing toluene for 2 h gave **10** as the only isomer in 34% yield. In contrast to pyrones **3** and **6**, less reactive amide **9** reacts with phenylhydrazine in EtOH to produce 3-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1*H*-pyrazole-5-carboxamide **11** in 15% yield (Scheme 3). In this case, the reaction in dioxane or toluene does not produce a pyrazole derivative, and gives a complex mixture of products instead.

Sodium 6-(trifluoromethyl)comanoate **12** is a more reactive γ-pyrone than amide **9** towards phenylhydrazine. Treatment of **12** with excess phenylhydrazine in water at 20 °C for two days afforded the sodium salt **13** as a solvate with two molecules of phenylhydrazine (22% yield), which could be transformed into carboxylic acid **4** by heating in dilute HCl (81% yield) (Scheme 4). The structure of **13** was confirmed by ^1H, ^{13}C NMR (DMSO-d_6), IR, EI-MS spectroscopies and elemental analysis. In the ^1H NMR spectrum, 20 aromatic protons, one pyrazole proton as a singlet at δ 6.48 and a singlet due to two methylene protons at δ 4.06 were observed. In the EI-MS, fragmentation of **13** occurred as a cluster of ion peaks $[2{\cdot}387^- + 2H^+ + Na^+]^+$, $[387^- + 2Na^+]^+$, $[387^- + H^+ + Na^+]^+$, $[387^- + 2H^+]^+$. This spectrum demonstrates the existence of the pyrazolyl carboxylate anion of molecular weight 387.

The strong solvent influence on the reaction route can be explained as follows: in a protic medium, phenylhydrazine attacks predominantly at position 2 of the pyrone ring, rather than at the carbonyl carbon atom (Scheme 5). In this case, the formation of intermediate **A** is facilitated by protonation of the carbonyl oxygen atom with a solvent molecule. The trifluoromethyl group could also influence the stability of **A** due to hyperconjugation between the C–F bonds and the diene moiety. In an aprotic solvent the reaction pathway includes attack of phenylhydrazine at the carbonyl carbon. This attack is facilitated by a possible intramolecular proton transfer in transition state **B** without participation of the solvent.

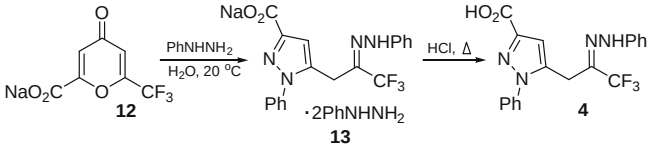
We also found that the trifluoromethyl group in pyrazole **7** and its solvate **8** could be easily hydrolyzed into a carboxylic function by treatment with KOH in EtOH to give the corresponding dipotassium salt **14**. A possible mechanism for the facile substitution of the fluorine atoms in these compounds includes elimination of HF by deprotonation of the NH group with hydroxide (ethoxide) (Scheme 6). Treatment of **14** with HCl gave the corresponding dicarboxylic acid **15** in 85% yield. The structure of **15** (monohydrate) and its dipotassium salt was confirmed by ^1H NMR and IR spectroscopies, and elemental analysis. The ^1H NMR spectrum (DMSO-d_6) of **15** showed two broad signals for the protons of the carboxylic groups at δ 12.5–14.0.

The signal of the deshielded NH proton at about δ 12.0 proves that this proton forms an intramolecular hydrogen bond (IHB) with the oxygen of the carbonyl group (for compounds **4**, **5**, **7** and **11**, the corresponding narrow signal was observed at δ 10.27–10.30). The presence of an IHB confirms the *Z*-isomeric structure of the dicarboxylic acid **15**. Treatment of **14** with HCl under harsher con-



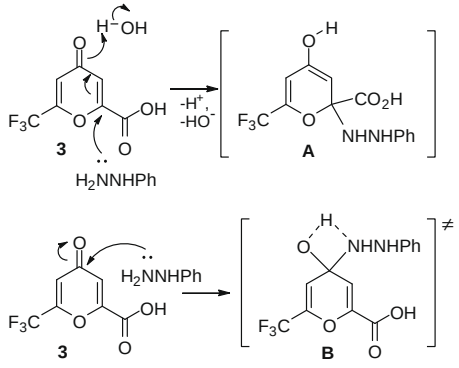
7 **8** **6** (R = OEt) **9** (R = NH_2) **10** **11**

Scheme 3.



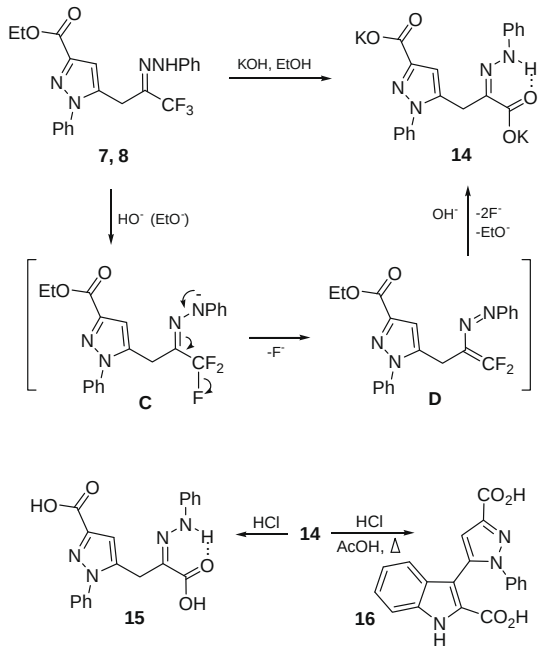
12 **13** **4**

Scheme 4.



3 **A** **3** **B**

Scheme 5.



Scheme 6.

Table 1
Synthesis of the pyrazole derivatives

Entry	Substrate	Solvent	Product	Yield (%)	Mp (°C)
1	**3**, **13**	H_2O	**4**[5]	64,[a,b] 81[c]	230–232
2	**3**	Dioxane	**5**[6]	30	222–223
3	**3**	Toluene	**4** + **5** (1:2)	45	201–204
4	**6**	EtOH	**7**	43	199–200
5	**6**	EtOH	**8**	69	106
6	**6**	Toluene	**10**	34	106
7	**9**	EtOH	**11**	15	201–203
8	**12**	H_2O	**13**	22	218–220
9	**7**, **8**	EtOH–H_2O	**14**	23,[d] 69[e]	239–242
10	**14**	H_2O	**15**	85	186–187
11	**14**	AcOH–H_2O	**16**	63	281–282

[a] Reagent: $PhNHNH_2$·HCl.
[b] Prepared from **3**.
[c] Prepared from **13**.
[d] Prepared from **7**.
[e] Prepared from **8**.

ditions (heating in AcOH–H_2O) resulted in the formation of the Fischer reaction product, pyrazolyl-indole derivative **16** with two carboxylic groups in 63% yield. The structure of **16** was proved to be the pyrazolyl-indole by conventional spectroscopic methods.

Facile nucleophilic substitution of α-fluorine atoms in phenylhydrazones of trifluoromethylketones is not known (Knunyants and Bargamova[4] described substitution of α-fluorine atoms in phenylhydrazones of fluoroalkyl aldehydes under the action of phenylhydrazine molecules; hydrolysis reactions of the α-difluoromethylene group in these hydrazones were not described). Importantly, solvate **8** is more reactive to hydrolysis than **7** and gives a higher yield of **14** (Table 1, entry 9). It should be noted that no hydrolysis products were isolated when the same reaction was conducted using pyrazoles **4**, **5**, **10** and **11**.

In summary, we have demonstrated novel regioselective solvent-sensitive reactions of 6-(trifluoromethyl)comanic acid and its derivatives, which give a number of highly functionalized derivatives of 1-phenyl-1*H*-pyrazole-5-carboxylic acids and 1-phenyl-1*H*-pyrazole-3-carboxylic acids. These results are of interest for the development of the chemistry of trifluoromethylated (fluoroalkylated) γ-pyrones.

Acknowledgement

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5. *Synthesis of 5-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1H-pyrazole-3-carboxylic acid* (**4**). A mixture of **3** (1.0 g, 4.8 mmol) and $PhNHNH_2$·HCl (1.53 g, 10.6 mmol) was refluxed in 5% aqueous HCl (10 mL) for 10 min. After cooling, the residue was filtered off and recrystallized from toluene (150 mL). Yield 64%, mp 230–232 °C, colourless solid.
IR (KBr) 3271, 1694, 1602, 1496 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.05 (s, 2H, CH_2), 6.46 (s, 1H, H-4), 6.93 (tt, 1H, H-4́, *J* = 7.3, 1.1 Hz), 7.17 (dd, 2H, H-2́, H-6́, *J* = 8.6, 1.1 Hz), 7.30 (dd, 2H, H-3́, H-5́, *J* = 8.6, 7.3 Hz), 7.51 (tt, 1H, H-4́, *J* = 7.1, 1.5 Hz), 7.59 (t, 2H, H-3́, H-5́, *J* = 7.6 Hz), 7.63 (dd, 2H, H-2́, H-6́, *J* = 8.5, 1.5 Hz), 10.30 (s, 1H, NH), 12.5–13.8 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.38 (t, CH_2, *J* = 131.3 Hz), 108.21 (dt, C4, *J* = 178.5, 3.1 Hz), 113.46 (dt, C2́, C6́, *J* = 161.0, 6.5 Hz), 121.27 (dt, C4́, *J* = 160.6, 7.8 Hz), 121.94 (qt, CF_3, $^1J_{C,F}$ = 272.4, 4.2 Hz), 124.98 (ddd, C2́, C6́, *J* = 164.1, 7.7, 4.2 Hz), 125.83 (qt, C=N, $^2J_{C,F}$ = 33.7 Hz, ^2J = 3.5 Hz), 128.76 (dt, C4́, *J* = 163.4, 6.8 Hz), 129.19 (ddd, C3́, C5́, *J* = 159.4, 8.0, 1.3 Hz), 129.44 (ddd, C3́, C5́, *J* = 163.5, 7.5, 1.5 Hz), 137.81 (dt, C5, *J* = 8.6, 7.9 Hz), 138.63 (t, C1́, *J* = 7.8 Hz), 143.77 (m, C1́), 144.51 (d, C3, *J* = 3.7 Hz), 162.98 (s, C=O). Anal. Calcd for $C_{19}H_{15}F_3N_4O_2$: C, 58.76; H, 3.89; N, 14.43. Found: C, 58.49; H, 3.81; N, 14.64.
6. *Synthesis of 3-[3,3,3-trifluoro-2-(phenylhydrazono)propyl]-1-phenyl-1H-pyrazole-5-carboxylic acid* (**5**). A mixture of **3** (1.0 g, 4.8 mmol) and freshly distilled $PhNHNH_2$ (1.15 g, 10.6 mmol) was refluxed in dry dioxane (30 mL) for 1.5 h. After cooling, the solvent was evaporated and the residue was treated with 5% aqueous HCl (20 mL). The aqueous solution was decanted, the crude product triturated with CCl_4 and the solid was filtered off. Yield 30%, mp 222–223 °C, colourless solid.
IR (KBr) 3289, 1708, 1604, 1533, 1500 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 4.02 (s, 2H, CH_2), 6.84 (s, 1H, H-4), 6.90 (tt, 1H, H-4́, *J* = 7.3, 1.1 Hz), 7.19 (dd, 2H, H-2́, H-6́, *J* = 8.6, 1.1 Hz), 7.28 (dd, 2H, H-3́, H-5́, *J* = 8.6, 7.3 Hz), 7.40–7.49 (m, 5H, Ph), 10.29 (s, 1H, NH), 13.37 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 23.16 (t, CH_2, *J* = 131.3 Hz), 111.34 (dt, C4, *J* = 179.1, 2.8 Hz), 113.32 (dt, C2́, C6́, *J* = 161.1, 6.7 Hz), 120.97 (dt, C4́, *J* = 160.3, 7.1 Hz), 122.13 (q, CF_3, $^1J_{C,F}$ = 272.4 Hz), 125.57 (d, C2́, C6́, *J* = 163.1 Hz), 128.60 (q, C=N, $^2J_{C,F}$ = 32.9 Hz), 128.22 (dt, C4́, *J* = 162.1, 7.5 Hz), 128.50 (ddd, C3́, C5́, *J* = 162.7, 7.0, 1.8 Hz), 129.14 (ddd, C3́, C5́, *J* = 159.7, 7.9, 1.5 Hz), 134.90 (d, C5, *J* = 7.7 Hz), 139.90 (t, C1́, *J* = 8.3 Hz), 144.02 (t, C1́, *J* = 7.8 Hz), 146.22 (m, C3), 159.69 (d, C=O, *J* = 0.9 Hz). Anal. Calcd for $C_{19}H_{15}F_3N_4O_2$: C, 58.76; H, 3.89; N, 14.43. Found: C, 58.54; H, 3.77; N, 14.61.