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Methyl 3,3,3-trifluoropyruvate hemiaminals: Stability and transaminations

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Abstract

Hemiaminals of methyl 3,3,3-trifluoropyruvate with aromatic amines, benzylic monoamines and diamines were prepared and their interconversions studied using NMR spectrometry. In solution, benzylic hemiaminals were found to be stable in contrast to aromatic hemiaminals, which, in turn, were stable in the solid state.

Keywords: Methyl 3,3,3-trifluoropyruvate; Methyl 3,3,3-trifluoro-2-oxopropanoate; Hemiaminal equilibrium; Trifluoromethyl synthon

1. Introduction

The building block strategy using simpler fluorinated compounds, which are relatively easily accessible and display appropriate reactivity, has been one of general ways for the introduction of fluoro substituents in target molecules. Methyl 3,3,3-trifluoropyruvate (**1**, MeTFP) can be included in the pool of fluorinated building blocks. Two reaction centers in MeTFP, i.e. the carbonyl and ester groups, predetermine it for the syntheses of trifluoromethylated heterocyclic compounds [1–3]. MeTFP has also been used for the preparation of acyclic compounds as trifluoromethylated amino acids and peptides [4,5].

The reactivity of MeTFP and that of its non-fluorinated analogue, methyl pyruvate, differ considerably. The reason is, as characterised by the Taft σ_I constants [6], a strongly electron-withdrawing trifluoromethyl group in MeTFP molecule, which is in a sharp contrast to the electron-donating methyl group [6] in methyl pyruvate (Scheme 1). The trifluoromethyl group thus significantly increases the electrophilicity of the oxo group in MeTFP. This property enables MeTFP to form relatively stable hemiketals and/or hemiaminals.

MeTFP forms hemiaminal compounds **3** by a non-catalysed nucleophilic addition of primary aliphatic amines or amides to the carbonyl group [7–10]. However, the adducts, hemiaminals **3**, have been characterised or isolated only in particular cases, viz. methylamine [7] and benzylamine [8] hemiaminals. The hemiaminals prepared from carboxamides [11–13] were applied in the syntheses of trifluoromethylated amino acid analogues and peptides [4,5]. Primary sulfonamides [14,15] and carbamates [14,16,17] react in an analogous way (Scheme 2).

Aromatic amines react with MeTFP in a more complex way to form four types of products (**A**–**D**, Scheme 3) depending on amine structure and reaction conditions. Hemiaminals **A**, i.e. the products of *N*-alkylations, are formed only with primary aromatic amines. The hemiaminal of aniline with MeTFP has been mentioned in several papers [18–20], but was not completely characterised and has been considered as unstable compound that slowly rearranged [21] to the products of *ortho*- and/or *para*-*C*-hydroxyalkylations (**B** and **C**). The mechanism of the formation of the rearranged products of *C*-hydroxyalkylations has not been established so far. A recent theoretical study [22] has also not given a satisfactory explanation. On the other hand,

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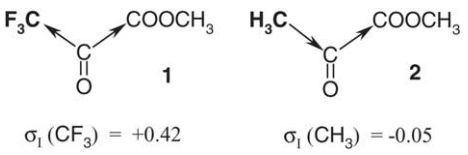
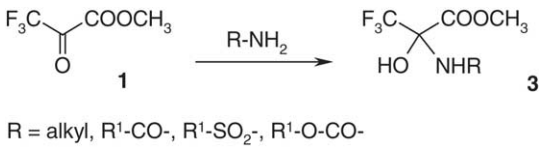


Scheme 1. Comparison of inductive effects in MeTFP and methyl pyruvate using Taft σ_I constants.



Scheme 2. Reactions of MeTFP (**1**) with nitrogen nucleophiles to form hemiaminals **3**.

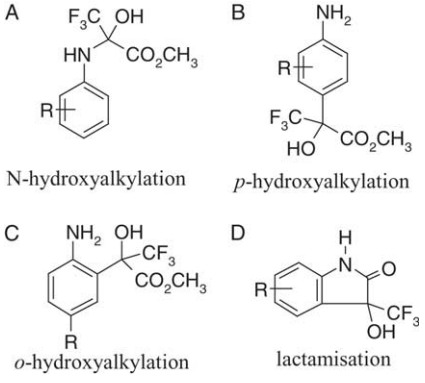
hemiaminals of aromatic amines **A** possessing an electron-withdrawing group, e.g. hemiaminal of 4-methyl-2-nitroaniline [18], did not rearrange at all. Hemiaminals of amines bearing alkylated *ortho*- and *para*-positions as 2,4,6-trimethylaniline [20] did not rearrange either. In particular cases, the products of the *ortho*-hydroxyalkylations **C** underwent lactamisation to form indolinones **D** [18,19].

We have studied the formation and stability of particular hemiaminals of MeTFP, including diamines, in the context of their usage as potential building blocks. We report our observations in this paper. Some of these hemiaminals have been applied in the syntheses of trifluoromethylated analogues of the alkaloid Peganine [23].

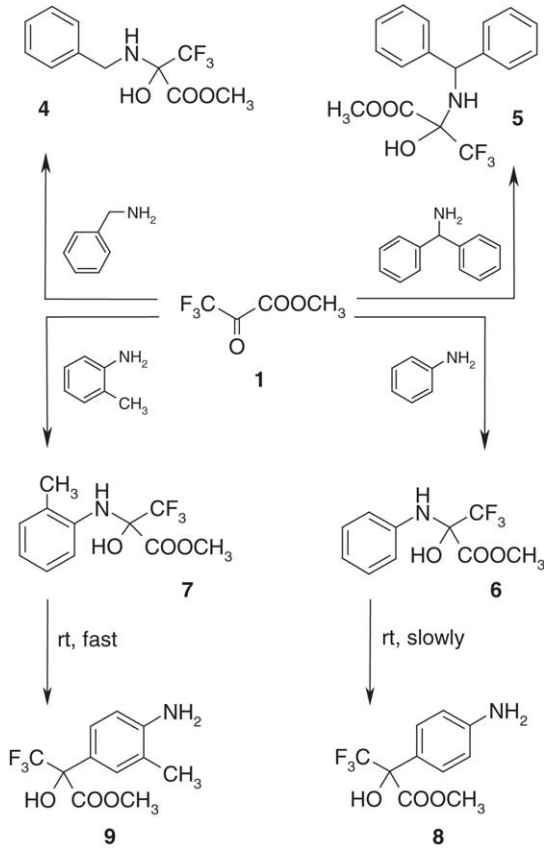
2. Results and discussion

2.1. Hemiaminals of anilines and benzylic monoamines

Hemiaminals of MeTFP with benzylamine (**4**), benzhydrylamine (**5**), aniline (**6**) and 2-methylaniline (**7**) were



Scheme 3. Types of the products formed by the reaction of MeTFP (**1**) with arylamines.



Scheme 4. Reactions of MeTFP (**1**) with primary aromatic and benzylic amines.

prepared (Scheme 4) to obtain their NMR characteristics for monitoring equilibration and competitive reactions (vide infra). The hemiaminals **4**–**7** were formed immediately and quantitatively after mixing the reagents. The compounds **4** and **5** are stable and can be purified by crystallization while the compounds **6** and **7** are unstable in solution and spontaneously undergo a rearrangement, which is probably of electrophilic character, to afford the corresponding products **8** [21] and **9** of *C*-hydroxyalkylation (Scheme 4). A special procedure for the preparation and isolation of the hemiaminal **6** was applied to isolate it in a crystalline form. In contrast to the literature information [21], crystalline **6** appears to be stable under inert atmosphere. Hemiaminal **7** rearranges much more rapidly in solution than hemiaminal **6** and therefore we failed to isolate it. Its presence in the reaction mixture was confirmed only by NMR but the product **9** of its subsequent rearrangement was completely characterised. Instability of hemiaminal **7** is obviously caused by the presence of the methyl group at the aromatic ring increasing its reactivity toward electrophiles. This assumption of the probable electrophilic character of the rearrangement has been supported by the recent publication on the application of MeTFP as an electrophilic reagent [24].

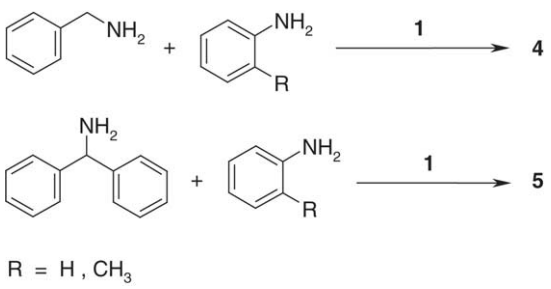
2.2. Equilibria of the reactions of methyl 3,3,3-trifluoropyruvate with monoamines

In the reaction of MeTFP with a diamine bearing two amino groups of different nucleophilicity, e.g. 2-aminobenzylamine, a hemiaminal can be formed potentially at aromatic or benzylic amino groups. To estimate the regioselectivity of the addition, some competitive reactions were carried out. The reaction of the mixture of benzylamine and aniline or 2-methylaniline led immediately to the hemiaminal of benzylamine (**4**). Analogously, the mixture of benzhydrylamine and aniline or 2-methylaniline afforded the hemiaminal of benzhydrylamine (**5**) immediately after mixing with MeTFP. The formation of the products of both reactions was very probably under kinetic control.

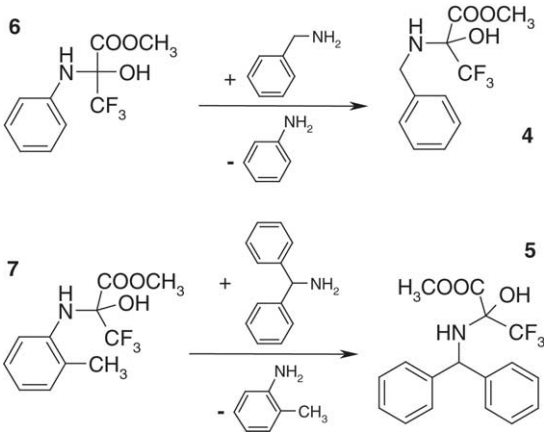
The question has arisen whether the products **4** and **5** can be formed also under thermodynamic control from the less stable hemiaminals **6** and **7** formed from aromatic amines, i.e. by a nucleophilic substitution at the hemiaminal carbon. In the experiments (Scheme 6), benzylic amines were added in parts to the solutions of hemiaminal **6** or **7**. As a result, the products **4** or **5** were formed rapidly (the reactions were followed by ^{1}H and/or ^{19}F NMR). The experiments depicted in Schemes 5 and 6 revealed that the more stable hemiaminals of benzylic amines are formed under thermodynamic control.

2.3. Equilibrium of the reactions of benzyl hemiaminal 4 with water

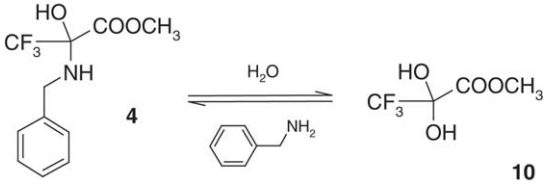
The stability of hemiaminal **4** towards water as a nucleophile was tested under equilibrium conditions (Scheme 7); water was portionwise added to the solution of hemiaminal **4** in DMSO-d_6 and the ratio of **4** and trifluoropyruvate hydrate **10** was checked repeatedly during 24 h to verify whether the equilibrium was established. It usually occurred within several minutes. The equilibrium constant was calculated on the basis of these measurements as 3×10^{-4}. The equilibrium data have revealed that hemiaminal **4** is practically stable in an aqueous solution.



Scheme 5. Competition of benzylic and aromatic primary amines for MeTFP (**1**).



Scheme 6. Transamination reactions of aromatic hemiaminals **6** and **7** (**1**).

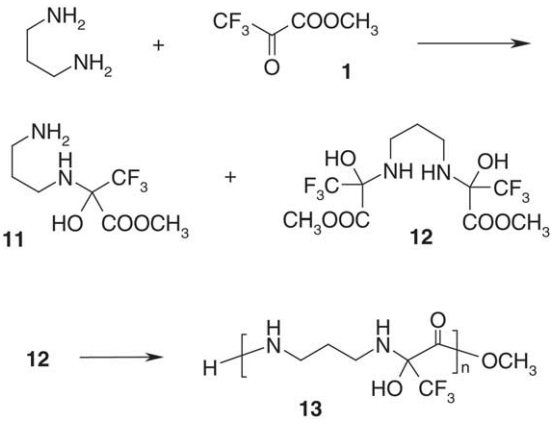


Scheme 7. Equilibrium reaction of hemiaminal **4** with water.

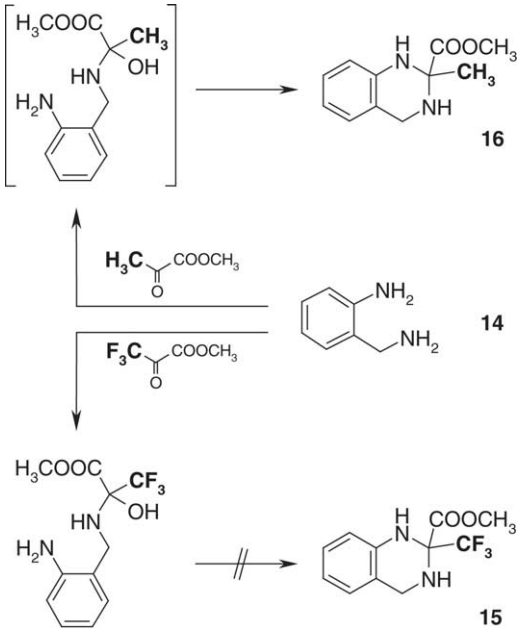
2.4. Reactions of methyl 3,3,3-trifluoropyruvate with diamines

2.4.1. Reaction with propane-1,3-diamine

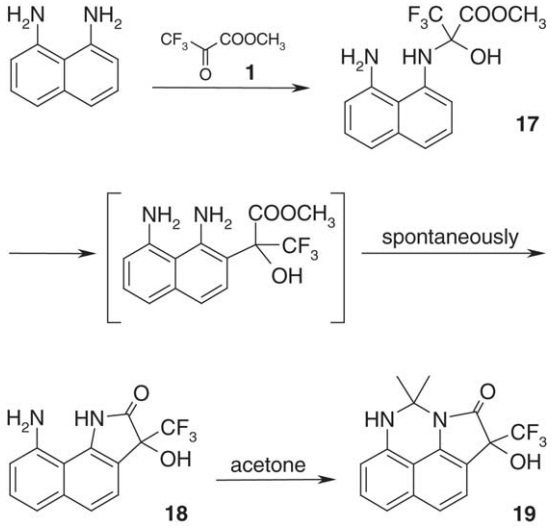
Propane-1,3-diamine forms the corresponding stable mono-hemiaminal **11** (Scheme 8) together with a small portion of bis-hemiaminal **12** (as a mixture of diastereoisomers **12a** and **12b**) immediately after mixing with MeTFP. Bis-hemiaminal **12** is stable in diluted solution, but during isolation while increasing its concentration in the solution, a precipitate of **13** insoluble in common organic solvents, is formed. The substance **13** is probably a polymer of a polyamide type as indicated by its IR spectrum.



Scheme 8. Reaction of propane-1,3-diamine with MeTFP (**1**) and probable polymer **13**.



Scheme 9. Different reaction of MeTFP (**1**) and methyl pyruvate with 2-aminobenzylamine.



Scheme 10. Transformation of naphthalene-1,8-diamine to tetracyclic heterocycle **19** using MeTFP (**1**) and acetone.

2.4.2. Reaction with 2-aminobenzylamine

2-Aminobenzylamine (**14**) affords the expected stable hemiaminal **15** immediately after mixing with MeTFP (Scheme 9). The reaction takes place at the more nucleophilic benzylic amino group (see Section 2.1) with complete regioselectivity. As depicted in Scheme 9, the reactivity of the non-fluorinated analogue of MeTFP, methyl pyruvate, differs from that of MeTFP: methyl pyruvate affords cyclic aminal **16** when reacted with 2-aminobenzylamine.

2.4.3. Reaction with naphthalene-1,8-diamine

Naphthalene-1,8-diamine affords unstable mono-hemiaminal **17** immediately after mixing with MeTFP (Scheme 10). The compound **17** is much less stable than the hemiaminal of 2-methylaniline (**7**, see Section 2.1), therefore its presence in the mixture could be confirmed only by ^{19}F NMR spectroscopy in a mixture. It is converted by an intramolecular reaction spontaneously into the product of the *ortho-C*-alkylation (type **C**, Scheme 3), which subsequently forms the lactam ring to afford the indolinone derivative **18** analogously to naphthalene-1-amine [18] (type **D**, Scheme 3). Indolinone **18** absorbed carbon dioxide as verified by elemental analysis. Therefore, it was reacted with acetone to give stable tetracyclic aminal **19**, which was completely characterised.

3. Experimental

General comments: The temperature data were not corrected. All reactions were performed in a well-dried distillation apparatus closed by a drying tube filled up with $CaCl_2$ and KOH and under argon atmosphere. The ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded at frequencies of 300, 282 and 76 MHz, respectively, on Varian Gemini 300 HC. Chemical shifts (δ) are given in ppm relatively to TMS for ^{1}H or ^{13}C and to $CFCl_3$ for ^{19}F NMR. The interaction constants (J) are given in Hz and if not mentioned otherwise J_{HH} is presented. $CDCl_3$ was used as a solvent if not mentioned otherwise. MS spectra were observed on a Hewlett-Packard MSD 5971A instrument (1989, EI 70 eV). Infrared spectra in KBr pellets were scanned on a NICOLET 740 USA apparatus. All reagents were purchased from Sigma–Aldrich and used without additional purifications with the exception of aniline. The solvents were purified and dried according to standard procedures.

*3.1. Reaction of MeTFP with aniline: methyl 2-anilino-3,3,3-trifluoro-2-hydroxypropanoate (**6**)*

A flask immersed in an ice bath was charged with diethyl ether (10 mL) and aniline (0.44 g, 4.7 mmol). MeTFP (1.80 g, 11.5 mmol) was then distilled from another flask into the reaction mixture, followed by stirring the mixture for 1 h. MeTFP was then removed from the mixture by distillation (oil bath, 140 °C) and the concentrated solution of the product **6** was immediately evaporated to dryness in vacuum on rotary evaporator to afford hemiaminal **6** (1.16 g, 100%) as a white solid, m.p. 66–68 °C. The compound was immediately subjected to spectral measurements and analyses and stored in a refrigerator.

^{1}H NMR ($CDCl_3$): δ 7.23 (2H, dd, 7.5, 8.5), 6.97 (1H, tt, 1.0, 7.4), 6.88 (2H, dd, 1.0, 8.2), 4.64 (1H, bs, temp), 4.48 (1H, bs, temp), 3.85 (3H, s). ^{13}C NMR ($CDCl_3$): δ 168.0, 141.0, 128.5 (2 × CH), 121.3 (CH), 121.2 (q, $^1J_{CF}$ = 288.5), 117.1 (2 × CH), 83.7 (q, $^2J_{CF}$ = 31.6), 53.9. ^{19}F NMR: δ −80.0 (s). LRMS (EI) (relative intensity, %): 249 (21, M^+), 210 (2), 190 (66), 180 (5), 120 (70), 93 (84), 92 (20), 78 (3),

69 (100), 66 (20), 65 (20), 59 (98), 50 (11). Anal. calc. for $C_{10}H_{10}F_3NO_3$: C, 48.2%; H, 4.05%; N, 5.6%; F, 22.9%. Found: C, 47.7%; H, 4.15%; N, 5.65%; F, 23.5%.

3.2. Reaction of MeTFP with 2-methylaniline (products 7 and 9)

Method A: The same procedure as that for **6**—2-methylaniline (0.30 g, 2.8 mmol), MeTFP (1.10 g, 7.0 mmol) and diethyl ether (15 mL). After evaporation, an oily compound was obtained. The NMR analysis showed that the mixture contained 55% of hemiaminal **7** and 45% of the product of the subsequent *p-C*-hydroxyalkylation, lactam **9**.

Method B: A NMR tube was charged with $CDCl_3$ (1 mL), MeTFP (0.25 g, 1.6 mmol) and a solution of 2-methylaniline (0.18 g, 1.7 mmol) in $CDCl_3$ (1 mL) was added in three portions. After each addition, the ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded to obtain the NMR signals of hemiaminal **7**. The progress of the subsequent rearrangement of **7**, which was followed by ^{19}F NMR, was completed in 13 days. The reaction mixture was then evaporated to dryness to obtain 452 mg of a yellow solid, which was purified on chromatographic column (silica gel, 2 g, chloroform) to afford 0.27 g (63%) of **9** as white solid, m.p. 141.5–142 °C.

Methyl 3,3,3-trifluoro-2-hydroxy-2-[(2-methylphenyl)amino]propanoate (**7**)

^{1}H NMR: δ 7.11 (1H, d, 7.7), 7.05 (1H, t, 7.7), 6.90 (1H, d, 7.7), 6.86 (1H, t, 7.7), 4.66 (2H, bs), 3.97 (3H, s), 2.23 (3H, s). ^{13}C NMR: δ 168.7, 140.1, 130.6 (CH), 128.8 (CH), 125.9, 121.9 (quin, $^1J_{CF}$ = 288.6), 121.6 (CH), 115.8 (CH), 84.5 (q, $^2J_{CF}$ = 31.5), 54.5, 17.2. ^{19}F NMR: δ −81.1 (s).

Methyl 2-(4-aminophenyl)-3,3,3-trifluoro-2-hydroxypropanoate (**9**)

^{1}H NMR: δ 7.40 (1H, s), 7.38 (1H, d, 8.7), 6.65 (1H, d, 8.3), 3.93 (3H, s), 3.78 (3H, bs, temp), 2.17 (3H, s). ^{13}C NMR: δ 169.9, 145.76, 128.7 (CH), 125.5 (CH), 123.2 (q, $^1J_{CF}$ = 285.5), 122.4, 121.9, 114.5 (CH), 77.7 (q, $^2J_{CF}$ = 32.8), 54.2 (CH_3), 17.4 (CH_3). ^{13}C dec-off NMR: 169.9 (q, J_{CH} = 4.0), 145.76 (m), 128.7 (dm, $^1J_{CH}$ = 157.8), 125.5 (dd, J_{CH} = 6.8, $^1J_{CH}$ = 160.8), 123.2 (q, $^1J_{CF}$ = 285.5), 122.4 (d, J_{CH} = 8.5), 121.9 (qui, J_{CH} = 5.6), 114.5 (d, $^1J_{CH}$ = 156.5), 77.7 (m), 54.2 (q, $^1J_{CH}$ = 149.0), 17.4 (dq, J_{CH} = 5.1, $^1J_{CH}$ = 126.5). ^{19}F NMR: δ −77.1 (s). IR (KBr): 1751 (s). LRMS: 263 (33, M^+), 224 (2), 205 (12), 204 (100), 195 (1), 194 (9), 135 (9), 134 (90), 107 (48), 106 (26), 79 (10), 78 (6), 77 (11), 69 (2), 67 (7), 65 (2), 59 (6), 53 (7), 50 (2). Anal. calc. for $C_{11}H_{12}F_3NO_3$: N, 5.3%. Found: N, 5.2%.

3.3. Reaction of MeTFP with benzhydrylamine: methyl 2-(diphenylmethyl)amino-3,3,3-trifluoro-2-hydroxypropanoate (5)

A flask (25 mL) was charged with benzhydrylamine (0.65 g, 3.5 mmol) and dry Et_2O (5 mL). A solution of MeTFP (0.61 g, 3.9 mmol) in dry Et_2O (5 mL) was then added dropwise while stirring. After 10 min, the mixture was evaporated to dryness to obtain 0.84 g (70%) of pure hemiaminal **5** (check by ^{1}H NMR), m.p. 52–55 °C (hexane).

^{1}H NMR: δ 7.37–7.19 (10H, m), 5.21 (1H, d, 3.2, temp), 4.31 (1H, bs, temp), 3.32 (3H, s), 2.78 (1H, bd, 2.8, temp). ^{13}C NMR: δ 168.8, 143.5, 141.7, 128.7 (2 × CH), 128.3 (4 × CH), 127.5 (CH), 127.3 (CH), 127.2 (2 × CH), 122.2 (q, $^1J_{CF}$ = 286.8), 84.8 (q, $^2J_{CF}$ = 31.4), 59.3 (CH), 53.7 (CH_3). ^{19}F NMR: δ −81.1 (s). Anal. calc. for $C_{17}H_{16}F_3NO_3$: C, 60.2%; H, 4.75%; N, 4.15%; F, 16.8%. Found: C, 60.05%; H, 4.7%; N, 4.2%; F, 17.1%.

3.4. Reaction of MeTFP with benzylamine: methyl 2-(benzyl)amino-3,3,3-trifluoro-2-hydroxypropanoate (4)

The same procedure as that for **5**: MeTFP (0.25 g, 1.6 mmol) and benzylamine (0.17 g, 1.5 mmol) afforded 0.33 g (81%) of pure hemiaminal **4** (check by ^{1}H NMR), m.p. 54–57 °C.

^{1}H NMR: δ 7.22–7.37 (5H, m), 4.51 (1H, bs, temp), 3.95 (1H, d, 12.9), 3.81 (3H, s), 3.70 (1H, d, 12.9), 2.46 (1H, bs, temp). ^{13}C NMR: δ 168.9, 138.5, 128.5 (2 × CH), 128.3 (2 × CH), 127.5 (CH), 122.2 (q, $^1J_{CF}$ = 287.6), 85.4 (q, $^2J_{CF}$ = 31.2), 54.3 (CH_3), 45.9 (CH_2). ^{19}F NMR: δ −80.5 (s). LRMS (EI) (relative intensity, %): 204 (2, $M^+ - 59$), 195 (1), 194 (1), 129 (3), 115 (4), 107 (66), 106 (88), 99 (8), 97 (7), 91 (35), 79 (33), 78 (18), 77 (19.5), 69 (100), 65 (7), 60 (5), 59 (92), 53 (6), 52 (6), 51 (17), 50 (17). Anal. calc. for $C_{11}H_{12}F_3NO_3$: C, 50.2%; H, 4.6%. Found: C, 50.0%; H, 4.9%.

3.5. Competitive reactions

A flask (10 mL) was charged with dry Et_2O (2 mL), 1 M equivalent of aniline or 2-methylaniline (1.7 mmol) and 1 M equivalent of benzylamine or benzhydrylamine (1.7 mmol). A solution of MeTFP (0.5 M equivalent) was then added to the mixture in three portions while stirring. The ^{1}H and/or ^{19}F NMR spectra of the mixture were recorded immediately after adding each portion of the MeTFP solution. After the addition of the last portion of MeTFP, only the hemiaminal of the more reactive amine was detected: benzylamine ≫ aniline, benzylamine ≫ 2-methylaniline, benzhydrylamine ≫ aniline and benzhydrylamine ≫ 2-methylaniline.

3.6. Substitution reactions

(a) In a NMR tube, benzylamine (72 mg, 0.67 mmol) was dissolved in $CDCl_3$ (0.5 mL) and solid hemiaminal **6** (0.17 g, 0.69 mmol) was added in three portions. After each addition, the ^{19}F NMR was recorded and immediate formation of hemiaminal **4** was detected.

(b) In a NMR tube, hemiaminal **7** was generated by mixing the solution of MeTFP (0.10 g, 0.64 mmol) in $CDCl_3$ (0.3 mL) and 2-methylaniline (68 mg, 0.64 mmol) in

$CDCl_3$ (0.3 mL). A solution of benzhydrylamine (0.12 g, 0.64 mmol) in $CDCl_3$ (0.3 mL) was then added immediately in two equal portions. ^{1}H NMR was recorded after each addition, which confirmed immediate formation of hemiaminal **5**.

(c) In a NMR tube, hemiaminal **4** (152 mmol) was dissolved in CD_3SOCD_3 (0.5 mL) then water or benzylamine were added and the ratio of hemiaminal **4** to hydrate of MeTFP (HTFP) **10** was determined by ^{19}F NMR. Mixtures: (1) 40 mmol of benzylamine (in the form of hemiaminal **4**) and 5.5 mol of water, the observed ratio of **4**:**10** was 87:13; (2) 40 mmol of **4** and 11.0 mol of H_2O, the ratio was 14:86; (3) 40 mmol of **4** and 16.5 mol of H_2O, the ratio was 13:87; (4) 243.3 mmol of **4** and 16.5 mol of H_2O, the ratio was 71:29. The equilibrium constant of 3×10^{-4} was calculated from these data.

3.7. Reaction of MeTFP with propane-1,3-diamine

A flask (2 L) was charged with dry Et_2O (900 mL), propane-1,3-diamine (0.17 g, 2.3 mmol) and a solution of MeTFP (0.36 g, 2.3 mmol) in dry Et_2O (100 mL) was added at room temperature while stirring. The immediate ^{19}F NMR analysis showed the presence of hemiaminal **11**, and bis-hemiaminal diastereoisomers **12a** and **12b** in a ratio of 6:2:2 in the reaction mixture. The same ratio was observed after 30 days keeping the mixture at room temperature. The mixture was then evaporated to dryness under vacuum without bath to afford polymeric **13** (0.39 g) as a white solid insoluble in common organic solvents.

Methyl 2-(3-aminopropyl)amino-3,3,3-trifluoro-2-hydroxypropanoate (**11**)

^{19}F NMR: δ −81.4 (s).

Dimethyl-3,3,3,3′,3′,3′-hexafluoro-2,2′-dihydroxy-(1,3-propandiyldiamino)dipropanoate (**13**)

Diastereoisomer (**12a**)

^{19}F NMR: δ −80.8 (s).

Diastereoisomer (**12b**)

^{19}F NMR: δ −80.9 (s).

Polymeric compound (**13**)

IR (KBr): 3324 m, 3280 m, 2967 w, 2945 w, 2907 w, 1675 s, 1550 m, 1491 w, 1443 w, 1384 w, 1306 w, 1273 m, 1252 m, 1209 s, 1180 s, 1122 s, 1067 w, 995 w, 840 w, 767 w, 711 w. Anal. calc. for decamer $C_{61}H_{94}F_{30}N_{20}O_{21}$: C, 36.4%; H, 4.7%; N, 13.9%; F, 28.3%. Found: C, 35.6%; H, 4.75%; N, 13.9%; F, 25.8%.

3.8. Reaction of MeTFP with 2-aminobenzylamine (product *15*)

A flask (50 mL) was charged with 2-ABA (0.51 g, 4.2 mmol) and dry Et_2O (15 mL) and a solution of MeTFP (0.64 g, 4.1 mmol) in dry Et_2O (5 mL) was added dropwise while stirring. After 15 min, the mixture was evaporated to dryness to obtain 1.12 g (98%) of pure hemiaminal **15** (check by ^{1}H NMR), m.p. 69.5–70.5 °C (cyclohexane).

Methyl 2-(2-aminobenzylamino)-3,3,3-trifluoro-2-hydroxypropanoate (**15**)

^{1}H NMR: δ 7.11 (1H, td, 7.7, 1.4), 7.00 (1H, d, 7.2), 6.72–6.66 (2H, m), 4.42 (3H, bs, temp), 3.91 (1H, dd, 12.1, 3.9, temp), 3.84 (3H, s), 3.60 (1H, dd, 12.1, 8.2, temp), 2.37 (1H, dd, 8.2, 3.9, temp). ^{13}C NMR: δ 168.5, 146.5, 130.3 (CH), 129.2 (CH), 122.0 (q, 287.4), 121.8, 118.1 (CH), 116.0 (CH), 85.3 (q, 31.3), 54.5 (CH_3), 44.4 (CH_2). ^{19}F NMR: δ −81.0 (s). Anal. calc. for $C_{11}H_{13}F_3N_2O_3$: C, 47.5%; H, 4.7%; N, 10.05%; F, 20.5%. Found: C, 47.8%; H, 4.9%; N, 9.9%; F, 20.45%.

3.9. Reaction of MeTFP with naphthalene-1,8-diamine (products *17* and *18*)

A solution of MeTFP (0.28 g, 1.8 mmol) in dry Et_2O (4 mL) was added dropwise to the stirred solution of naphthalene-1,8-diamine (0.29 g, 1.8 mmol) in dry Et_2O (4 mL). Immediately recorded ^{19}F NMR spectrum showed the presence of hemiaminal **17** and indolinone **18**. After 1 h, the content of indolinone **18** was 55 mol% and after additional 36 h, the complete conversion of hemiaminal **17** to indolinone **18** was observed. The mixture was then evaporated to dryness to afford a solid residue (0.41 g), which was purified by precipitation from methanol by chloroform to obtain 0.23 g (44%) of light brown crude indolinone **18**, m.p. 191–194 °C. A part of the solid was dried in vacuum (0.13 kPa) at 60 °C and subjected to all analyses. The second part (112 mg) was dissolved in acetone (15 mL) and dried over $MgSO_4$. After 16 days, the solution was filtered and evaporated to dryness to obtain 0.13 g of a yellow solid, which was purified on a chromatographic column (silica gel, 21 g, dichloromethane:acetone 95:5) to afford 0.10 g (81%) of pure **19** as yellow crystals, m.p. 163–165 °C (petroleum ether).

Methyl 2-[(8-aminonaphthalene-1-yl)amino]-3,3,3-trifluoro-2-hydroxypropanoate (**17**)

^{19}F NMR: δ −81.0 (s).

9-Amino-3-hydroxy-3-(trifluoromethyl)-1,3-dihydrobenzo[g]indol-2-one (**18**)

^{19}F NMR: δ −79.6 (s). ^{1}H NMR: δ 7.51 (1H, d, 8.4), 7.45 (1H, dd, 8.4, 0.5), 7.33 (1H, dd, 8.2, 1.0), 7.28 (1H, dd, 8.2, 7.3), 6.91 (1H, dd, 7.2, 1.1). ^{13}C APT NMR: δ 175.2, 144.6, 140.6, 138.6, 129.0 (CH), 125.0 (q, $^1J_{CF} = 284.4$), 124.0 (CH), 122.9 (CH), 121.9 (CH), 119.8, 116.3 (CH), 115.6, some signals did not appear. IR: 3361 w, 3306 w, 3242 w, 1727 s, 1636 w, 1614 w, 1587 w, 1457 w, 1424 m, 1273 m, 1257 m, 1202 m, 1188 m, 1179 m, 1163 m, 1144 m, 994 w, 942 w, 886 w, 861 w, 835 w, 828 w, 791 w, 763 w, 730 w, 691 w, 654 w, broad bands in region 2400–3000 can be assigned to absorbed CO_2. Anal. calc. for crude $C_{13}H_9F_3N_2O_2 + CO_2$: C, 51.55%; H, 2.8%; N, 8.6%; F, 20.5%. Found: C, 51.0%;

H, 3.0%; N, 8.9%; F, 20.45%. Anal. calc. after drying for $C_{13}H_9F_3N_2O_2$: C, 55.35%; H, 3.2%; N, 9.95%. Found: C, 54.8%; H, 3.65%; N, 9.7%.

4-Hydroxy-2,2-dimethyl-4-trifluoromethyl-1,2,3,4-tetrahydroindolo[1,7a,7,6-c,d,e]quinazolin-3-one (**19**)

^{1}H NMR: δ 7.54 (1H, d, 8.3), 7.49 (1H, d, 8.2), 7.40 (1H, dd, 8.3, 7.7), 7.29 (1H, d, 8.2), 6.64 (1H, d, 7.1), 3.94 (1H, bs), 1.95 (3H, s), 1.67 (3H, s), 0.66 (1H, bs). ^{13}C NMR: δ 172.1, 137.7, 137.3, 136.6, 129,7 (CH), 122.5 (CH), 123.1 (q, $^1J_{CF}$ = 285.7), 121.3 (CH), 117.5 (CH), 112.2, 109.3, 106.9 (CH), 77.5 (q, $^2J_{CF}$ = 32.1), 70.2, 26.9, 26.3. IR: 3390 m, 1724 s, 1653 w, 1607 m, 1443 w, 1191 s, 1172 s, 1135 m. Anal. calc. for $C_{16}H_{13}F_3N_2O_2$: C, 59.6%; H, 4.1%; N, 8.7%. Found: C, 59.3%; H, 4.4%; N, 8.7%.

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