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Simple Synthesis of 6-(Trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran Derivatives by One-Pot, Three-Component Reactions

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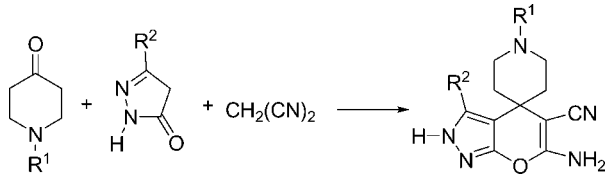
One-pot, three-component condensation reactions of aromatic aldehydes **1**, 3-methylpyrazol-5-one (**2**) and ethyl trifluoroacetoacetate (**3**) provided an efficient methodology for the preparation of ethyl (4*S**,5*R**)-4-aryl-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]-pyran-5-carboxylate derivatives (**4**). The reactions gave moderate to good yields under mild conditions. These new products **4** were fully characterized by spectral methods and single-crystal X-ray diffraction analysis. A plausible reaction pathway for the formation of **4** is presented.

Introduction

Fluorine-containing compounds have attracted much interest because of their unique chemical, physical and biological activities.[1–3] In particular, fluorine-containing heterocycles are now widely recognized as important organic molecules showing interesting biological activities with potential for applications in the medicinal and agricultural fields.[4,5] β-Keto esters are well established as synthetic intermediates in heterocyclic chemistry,[6] while the reactions of fluorinated 1,3-dicarbonyl compounds as fluorine-containing building blocks have been investigated extensively;[7,8] condensation of ethyl trifluoroacetoacetate with aldehydes resulting in the formation of 2-arylmethylene-substituted trifluoroacetoacetic esters has been reported, for example.[9] Meanwhile, the increasing environmental consciousness of the chemical community has given rise to the search for more efficient and environmentally friendly methods for chemical syntheses. Among these, multi-component reactions (MCRs), which belong to the most efficient methods for the preparation of heterocyclic compounds, by virtue of their convergence, productivity, ease of execution, and generally high yields of products, have attracted much attention from the vantage point of combinatorial chemistry.[10]

Evans and co-workers reported a one-pot, three-component synthesis of substituted 2*H*,4*H*-dihydropyrazolo-[3,4-*b*]pyrans from piperidin-4-ones, pyrazol-5-ones and malononitrile (Scheme 1).[11] More recently, our group have also successfully prepared 2-trifluoromethyl-3,4-dihydro-2*H*-pyran derivatives through reactions between ethyl trifluoroacetoacetate and arylidenemalononitriles.[8]



Scheme 1.

In continuation of our study of syntheses of fluorinated heterocycles, here we wish to report recent studies on one-pot, three-component syntheses of ethyl (4*S**,5*R**)-4-aryl-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylates (**4**) by condensation of compounds **1**, **2** and **3** in MeOH at reflux in the presence of catalytic amounts of piperidine.

Results and Discussion

Firstly, a stepwise reaction between ethyl trifluoroacetoacetate (**3**) and 4-arylidene-3-methylpyrazol-5-ones **5**, derived from condensation of arylaldehydes **1** with 3-methylpyrazol-5-ones **2**, was briefly investigated (Scheme 2).

A mixture of ethyl trifluoroacetoacetate (**3**) and a 4-arylidene-3-methylpyrazol-5-one **5** in MeOH (5 mL) was heated at reflux with stirring in the presence of piperidine (0.5 equiv.) for 5 h. TLC analysis showed that the reaction occurred, but use of a prolonged reaction time did not improve the yield significantly. Conventional workup afforded the compound **4a** in 58% yield.

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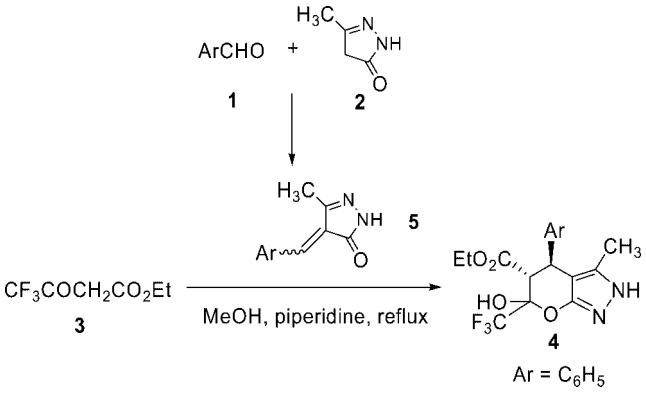


Scheme 2. A stepwise reaction for syntheses of compounds **4**.

Table 1. Optimization of the reaction conditions for the synthesis of **4b**.[a]

Entry	Solvent	Base (0.5 mol-equiv.)	Temp.	Yield (%)[b]
1	C_2H_5OH	Et_3N[c]	room temp.	27
2	C_2H_5OH	Et_3N[c]	78 °C	38
3	CH_3CN	Et_3N[c]	room temp.	36
4	CH_3CN	Et_3N[c]	82 °C	43
5	CH_3OH	Et_3N[c]	room temp.	40
6	CH_3OH	Et_3N[c]	65 °C	48
7	CH_3OH	DMAP[c]	65 °C	39
8	CH_3OH	DBU[c]	65 °C	57
9	CH_3OH	DABCO[c]	65 °C	41
10	CH_3OH	piperidine[c]	65 °C	60
11	CH_3OH	piperidine[d]	65 °C	62

[a] Compounds **1** (1 mmol), **2** (1 mmol) and **3** (1 mmol) in solvent (5 mL), each reaction being run for 5 h. [b] Isolated yields. [c] 0.5 equiv. of base. [d] 1 equiv. of base.

Purification of products **4** was tedious because of the poor solubility of 4-arylidene-3-methylpyrazol-5-ones **5** in MeOH. Therefore, in view of the success of the above stepwise reaction, we gave some attention to one-pot, three-component reactions.

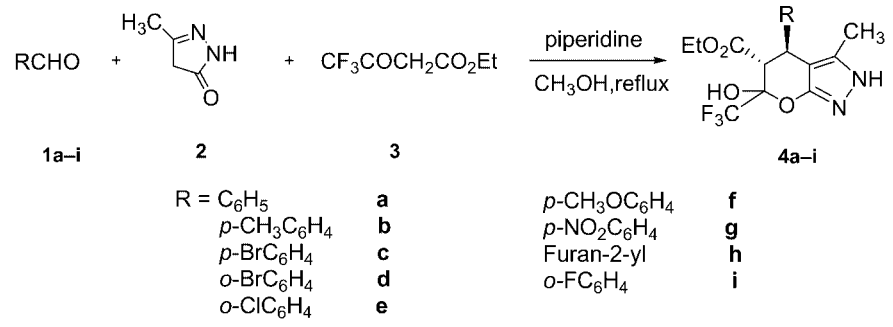
The one-pot, three-component reaction was simply carried out by mixing benzaldehyde (**1a**) with the other two components **2** and **3** in the presence of piperidine (0.5 equiv.) in MeOH (5 mL), and the resulting mixture was heated at reflux for 5 h. After removal of the solvent, column chromatography afforded the expected product **4a** in 60% yield.

On the basis of the above result, the effect of variation of the amine, including secondary and tertiary amines, on the efficiency and yield was investigated in detail. As shown in Table 1, of five amines, piperidine gave the highest yield (Entry 10, Table 1). Meanwhile, the effect of the solvent on the yield was also briefly studied. The reaction gave better yields in methanol as solvent than in ethanol or acetonitrile because methanol provided better solubility of compound **2**. Obviously, increasing of the reaction temperature to reflux gave better yields than the room temperature reactions (Entries 1–6, Table 1). In comparison, however, neither an increase in the amount of base piperidine from 0.5 equiv. (catalytic amount) to 1 equiv., nor the presence of excesses of 3-methylpyrazol-5-one (**2**; 1.2 equiv.) and aldehyde (**1b**; 1.2 equiv.) improved the yield drastically, whereas these measures caused trouble in separation and purification. It should be noted that no preliminary Michael addition product – in other words, the acyclic form of the product – was obtained under these conditions, due to the further intramolecular cyclization reaction affording the more stable cyclic compound. The reaction conditions and results are listed in Table 1.

Next, under the optimal conditions as shown in Entry 10 of Table 1, the one-pot three-component synthesis of various compounds **4** was performed (Scheme 3). Arylaldehydes bearing either electron-donating or electron-withdrawing groups were used as the substrates, the reactions proceeded successfully, and the corresponding products **4** were obtained in moderate to good yields (43–84%). In the case of **1h**, where the furan-2-yl aldehyde was used as the substrate, however, the reaction should be carried out at room temperature. TLC analysis showed that the starting material **1h** decomposed quickly in reflux despite the fact that the reaction was carried out under nitrogen (Entry 8, Table 2). In contrast, pentafluorobenzaldehyde, a typical arylaldehyde, gave no expected product (Entry 10, Table 2). Similarly, aliphatic aldehydes such as *n*-butyraldehyde were engaged under these reaction conditions but unfortunately none of the expected products were obtained (Entry 11, Table 2). Furthermore, the stepwise reaction between ethyl trifluoroacetoacetate and 4-butylene-3-methylpyrazol-5-one, obtained from condensation of *n*-butyraldehyde with 3-methylpyrazol-5-one (**2**), was also investigated, but the subsequent Michael addition and intramolecular cyclization reaction did not occur successfully.

The structures of the expected products **4** were assigned by spectroscopic analysis. The coupling constant of the vicinal six-membered ring protons in **4b** was 11.7 Hz, which indicated a *trans* configuration of the vicinal hydrogen atoms.[12] This kind of stereoselectivity was attributed to the two larger groups occupying *trans* positions, resulting in the formation of a more stable product during the intramolecular cyclization reaction. It was noteworthy that the proton signal of N–*H* was not visible either in $CDCl_3$ or in CD_3OD, but was discernible at δ = 11.85 ppm in [D_6]-DMSO. In its ^{19}F NMR spectrum, the chemical shift of the CF_3 group of **4b** was a singlet peak at δ = –83.57 ppm, indicating that CF_3 group was attached to the saturated sp^3 carbon atom, so the only possible configuration of **4b** is a hemiketal cyclic structure, in which the CF_3 group occupied the position *trans* to the ethoxycarbonyl group.

The absolute structures of **4** could not be assigned on the basis of ^1H NMR spectra, however, due to the tautomerization. In order to determine the structures of this series of compound definitively, that of **4h** was further confirmed by the single-crystal X-ray crystallographic study (Figure 1). A fine crystal suitable for XRD analysis was obtained by recrystallization of the pure compound from petroleum and acetone. It was unambiguously observed that the protons



Scheme 3. A one-pot, three-component reaction for the synthesis of compounds **4**.

Table 2. Preparation of 6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran derivatives **4**.[a]

Entry	Reactant	Temp. (°C)	Time (h)	Product **4**
1	**1a**: R = C_6H_5	65	4	**4a**
2	**1b**: R = *p*-$CH_3C_4H_6$	65	5	**4b**
3	**1c**: R = *p*-BrC_6H_4	65	6	**4c**
4	**1d**: R = *o*-BrC_6H_4	65	4	**4d**
5	**1e**: R = *o*-ClC_6H_4	65	4	**4e**
6	**1f**: R = *p*-$CH_3OC_4H_6$	65	4	**4f**
7	**1g**: R = *p*-$NO_2C_6H_4$	65	3	**4g**
8	**1h**: R = furan-2-yl	room temp.[b]	8	**4h**
9	**1i**: R = *o*-FC_6H_4	65	4	**4i**
10	**1j**: R = C_6F_5	65	5	–
11	**1k** R = *n*-C_3H_7	65	5	–

[a] Reaction conditions: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), piperidine (0.5 mmol). [b] Under reflux condition **1h** decomposed quickly.

had transferred from *N*(1) to *N*(2) to afford the more stable compounds **4**, without the formation of the tautomeric form **4′** (Scheme 4). This result was in accordance with the previous reported nonfluorinated substrates.[11] The selected bond lengths and bond angles of **4h** are listed in Table 3.

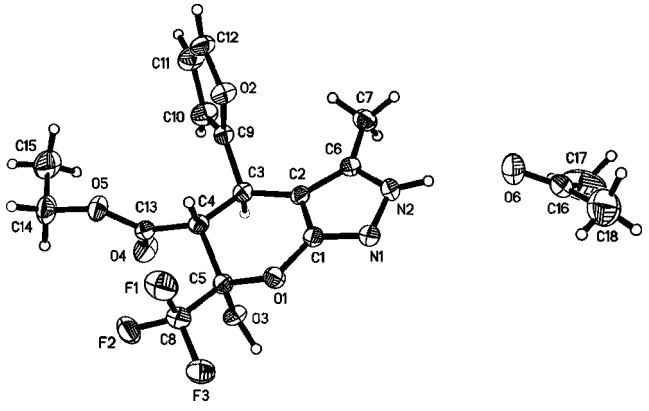
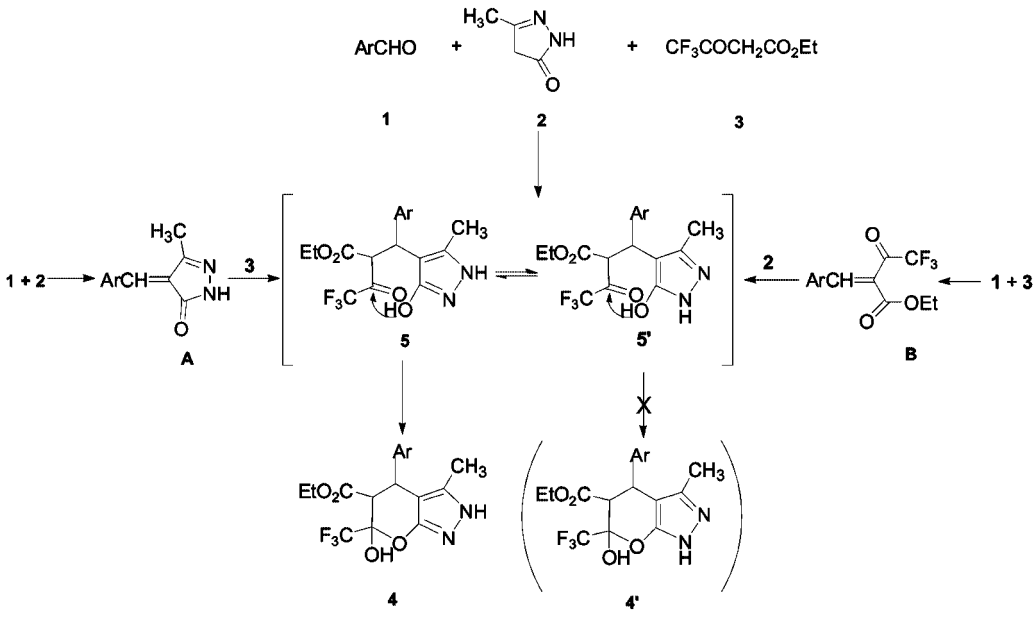


Figure 1. ORTEP view of **4h**.

It should be noted that all the products were recrystallized with petroleum ether/acetone to give the pure compounds and that, in some cases, fine crystals were obtained. However, in the cases of **4d**, **4e** and **4h,** the expected products were each complexed with one equivalent of acetone after recrystallization. ^{1}H NMR and microanalysis confirmed the presence of one equivalent of acetone in the crystals; the ^{1}H NMR spectra of **4d**, **4e** and **4h**, for instance, each showed, apart from the expected signals corresponding to the products, a singlet peak at δ = 2.11 ppm (6 H), which corresponds to the acetone protons. Elemental analysis results also confirmed the presence of one equivalent of acetone in the crystals. Moreover, one equivalent of acetone was also detected in XRD analysis, as illustrated in Figure 1.

A plausible mechanism for the formation of compounds **4** was analogous to previously reported work:[11] it is proposed that it proceeds through an initial Knoevenagel reaction. The aromatic aldehydes **1** could react with **2** or **3** to form the corresponding condensation products **A** or **B**, and products **A** or **B** could then further react with the third component **3** or **2** to give the Michael addition intermediate **5**, which in turn could undergo intramolecular cyclization to afford the products **4**, without formation of tautomeric forms **4′** (Scheme 4).

However, our attempts to prepare the dehydrated products by the procedure developed for the synthesis of trifluoromethyl-substituted pyrazole derivatives failed,[7e] demonstrating an unusual stability of these fused heterocyclics. In contrast with α-hydroxy-tetrahydro-pyrindines, which smoothly eliminated water to form the corresponding 1,4-dihydropyridines,[13] the products **4** were unaffected by boiling concd. H_2SO_4, by P_2O_5 or by $POCl_3$/Py in toluene as solvent. The result was very similar to those observed in previously reported work[14] where the dehydration reaction was an elimination reaction in which the stability of the activated complex depended on the participation of the electron pair of the neighbouring heteroatom present in the heterocyclic ring. The more difficult dehydration of compounds **4** in relation to α-hydroxy-tetrahydro-pyrindines was a product of the weaker electron-donating strength of the oxygen atom in the pyran ring in relation to the nitrogen atom in the pyrindine.



Scheme 4. Plausible mechanism for formation of compounds **4**.

Table 3. Selected bond lengths [Å] and bond angles [°] in **4h**.

Bond length [Å]		Bond angles [°]	
O(1)–C(1)	1.365(2)	C(1)–O(1)–C(5)	113.38(13)
O(1)–C(5)	1.427(2)	C(1)–N(1)–N(2)	101.85(15)
N(1)–C(1)	1.319(2)	C(6)–N(2)–N(1)	113.44(16)
N(1)–N(2)	1.370(2)	N(1)–C(1)–O(1)	119.54(15)
N(2)–C(6)	1.343(2)	N(1)–C(1)–C(2)	114.29(17)
C(1)–C(2)	1.388(2)	O(1)–C(1)–C(2)	126.13(16)
C(2)–C(6)	1.372(2)	C(6)–C(2)–C(1)	104.11(16)
C(2)–C(3)	1.495(2)	N(2)–C(6)–C(2)	106.30(16)

Conclusions

In conclusion, we have developed a one-pot reaction for the synthesis of 6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran derivatives from easily available starting materials. The reaction was applicable to a range of aldehydes with a variety of versatile functional groups. It should be noted that some of the products were complexed with one equivalent of acetone. Compounds **4** were unusually stable and resisted dehydration.

Experimental Section

Melting points were measured in a Melt-Temp apparatus and were uncorrected. ^{1}H NMR and ^{19}F NMR spectra were recorded in $CDCl_3$ on Bruker AM 300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Low-resolution mass spectra were obtained on a Finnigan GC-MS 4021 by the electron impact ionization technique (70 eV). Elemental analyses were performed at this institute.

General Procedure for the Preparation of 4a–h: A mixture of arylaldehyde **1** (1 mmol), **2** (98 mg, 1 mmol), **3** (184 mg, 1 mmol) and 0.5 equiv. of piperidine (42.5 mg, 0.5 mmol) in methanol (5 mL) was heated at reflux for the time specified (see in Table 2), except in the case of **1h**, which was stirred at room temperature, after which TLC analysis showed the reaction to be finished. The solvent was evaporated and the residue was chromatographed on a silica column with petroleum ether/ethyl acetate (1:1, v/v) as eluent to afford the product **4**. The solid products were recrystallized from petroleum ether/acetone to give the pure compounds.

Ethyl (4*S,5*R**)-6-Hydroxy-3-methyl-4-phenyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4a):** This compound (256 mg, 69%) was obtained as a white solid with m.p. 191–192 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H, ArH), 4.30 (d, J = 11.7 Hz, 1 H, CH), 3.98 (q, J = 7.2 Hz, 2 H, CH_2), 3.10 (d, J = 11.7 Hz, 1 H, CH), 1.63 (s, 3 H, CH_3), 0.94 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.53 (s, 3 F, CF_3) ppm. EI-MS (70 eV): *m*/*z* (%) = 370 (1) $[M]^+$, 369 (1) $[M - 1]^+$, 351 (3) $[M - 1 - H_2O]^+$, 186 (64) $[M - CF_3COCH_2CO_2Et]^+$, 185 (100) $[M - 1 - CF_3COCH_2CO_2Et]^+$, 109 (48) $[M - CF_3COCH_2CO_2Et - C_6H_5]^+$, 69 (64) $[CF_3]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3334, 2922, 1727, 1603, 1497, 1178, 1022, 701, 424 cm^{-1}. $C_{17}H_{17}F_3N_2O_4$ (370.32): calcd. C 55.14, H 4.63, N 7.56; found: C 55.18, H 4.61, N 7.45.

Ethyl (4*S,5*R**)-6-Hydroxy-3-methyl-4-tolyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4b):** This compound (226 mg, 60%) was obtained as a white solid with m.p. 202–203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.07 (m, 4 H, ArH), 4.25 (d, J = 11.7 Hz, 1 H, CH), 4.00 (q, J = 7.2 Hz, 2 H, CH_2), 3.06 (d, J = 11.7 Hz, 1 H, CH), 2.34 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 0.96 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.57 (s, 3 F, CF_3) ppm. EI-MS (70 eV): *m*/*z* (%) = 384 (2) $[M]^+$, 365 (5) $[M - 1 - H_2O]^+$, 201 (100) $[M + 1 - CF_3COCH_2CO_2Et]^+$, 200 (58) $[M - CF_3COCH_2CO_2Et]^+$, 185 (51) $[CF_3COHCH_2CO_2Et]^+$, 109 (50) $[M - CF_3COCH_2CO_2Et - C_7H_7]^+$, 69 (75) $[CF_3]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3338, 2924, 1728, 1602, 1500, 1177, 1021, 424 cm^{-1}. $C_{18}H_{19}F_3N_2O_4$ (384.35): calcd. C 56.25, H 4.98, N 7.29; found: C 56.09, H 4.92, N 7.31.

Ethyl (4*S,5*R**)-4-(4-Bromophenyl)-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4c):** This compound (246 mg, 57%) was obtained as a white solid with m.p. 172–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (d, J =

7.2 Hz, 2 H, ArH), 7.11 (d, J = 7.2 Hz, 2 H, ArH), 4.31 (d, J = 11.4 Hz, 1 H, CH), 3.99 (q, J = 7.2 Hz, 2 H, CH_2), 3.03 (d, J = 11.4 Hz, 1 H, CH), 1.69 (s, 3 H, CH_3), 1.00 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.39 (s, 3 F, CF_3) ppm. EI-MS (70 eV): m/z (%) = 266/264 (33/35) [M – $CF_3COCH_2CO_2Et]^+$, 265/263 (34/29) [M – 1 – $CF_3COCH_2CO_2Et]^+$, 185 (26) $[CF_3COHCH_2CO_2Et]^+$, 109 (100) [M – $CF_3COCH_2CO_2Et$ – $BrC_6H_4]^+$, 69 (86) $[CF_3]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3326, 2923, 1728, 1601, 1520, 1488, 1175, 1089, 1071, 1018, 730, 477 cm^{-1}. $C_{17}H_{16}BrF_3N_2O_4$ (449.22): calcd. C 45.45, H 3.59, N 6.24; found: C 45.23, H 3.58, N 6.02.

Ethyl (4*S,5*R**)-4-(2-Bromophenyl)-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4d):** This compound (380 mg, 84%) was obtained as a white solid with m.p. 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (d, J = 8.1 Hz, 1 H, ArH), 7.34–7.12 (m, 3 H, ArH), 5.04 (d, J = 11.4 Hz, 1 H, CH), 3.98 (q, J = 7.2 Hz, 2 H, CH_2), 3.17 (d, J = 11.4 Hz, 1 H, CH), 1.65 (s, 3 H, CH_3), 0.98 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.47 (s, 3 F, CF_3) ppm. EI-MS (70 eV): m/z (%) = 450/448 (1/1) $[M]^+$, 266/264 (23/29) [M – $CF_3COCH_2CO_2Et]^+$, 185 (100) $[CF_3COHCH_2CO_2Et]^+$, 69 (55) $[CF_3]^+$, 43 (44) $[CH_3CO]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3339, 2931, 1731, 1603, 1498, 1471, 1374, 1342, 1238, 1173, 1088, 1020, 751, 474 cm^{-1}. $C_{17}H_{16}BrF_3N_2O_4{\cdot}C_3H_6O$ (507.30): calcd. C 47.35, H 4.37, N 5.52; found: C 47.13, H 4.17, N 5.40.

Ethyl (4*S,5*R**)-4-(2-Chlorophenyl)-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4e):** This compound (209 mg, 51%) was obtained as a white solid with m.p. 124–125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.21 (m, 4 H, ArH), 5.06 (d, J = 11.7 Hz, 1 H, CH), 4.06 (q, J = 7.2 Hz, 2 H, CH_2), 3.15 (d, J = 11.7 Hz, 1 H, CH), 2.18 (s, 6 H, CH_3COCH_3), 1.68 (s, 3 H, CH_3), 0.99 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.43 (s, 3 F, CF_3) ppm. EI-MS (70 eV): m/z (%) = 405/403 (1/3) [M – 1]$^+$, 368 (1) [M – Cl]$^+$, 223/221 (11/33) [M + 1 – $CF_3COCH_2CO_2Et]^+$, 185 (100) $[CF_3COHCH_2CO_2Et]^+$, 69 (54) $[CF_3]^+$, 43 (89) $[CH_3CO]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3346, 2923, 1732, 1603, 1499, 1172, 1020, 752, 711, 423 cm^{-1}. $C_{17}H_{16}ClF_3N_2O_4{\cdot}C_3H_6O$ (462.85): calcd. C 51.90, H 4.79, N 6.05; found: C 51.81, H 4.89, N 5.66.

Ethyl (4*S,5*R**)-6-Hydroxy-4-(4-methoxyphenyl)-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4f):** This compound (173 mg, 43%) was obtained as a white solid with m.p. 182–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, J = 8.7 Hz, 2 H, ArH), 6.86 (d, J = 8.7 Hz, 2 H, ArH), 4.25 (d, J = 11.7 Hz, 1 H, CH), 4.01 (q, J = 7.2 Hz, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 3.06 (d, J = 11.7 Hz, 1 H, CH), 1.66 (s, 3 H, CH_3), 0.99 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.58 (s, 3 F, CF_3) ppm. EI-MS (70 eV): m/z (%) = 399 (1) [M – 1]$^+$, 217 (44) [M + 1 – $CF_3COCH_2CO_2Et]^+$, 109 (33) [M – $CF_3COCH_2CO_2Et$ – $CH_3OC_6H_4]^+$, 69 (100) $[CF_3]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3334, 2923, 1736, 1601, 1514, 1499, 1345, 1181, 1028, 822, 425 cm^{-1}. $C_{18}H_{19}F_3N_2O_5$ (400.35): calcd. C 54.00, H 4.78, N 7.00; found: C 53.61, H 4.44, N 6.77.

Ethyl (4*S,5*R**)-6-Hydroxy-3-methyl-4-(4-nitrophenyl)-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4g):** This compound (221 mg, 54%) was obtained as a white solid with m.p. 129–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.1 Hz, 2 H, ArH), 7.45 (d, J = 8.1 Hz, 2 H, ArH), 4.51 (d, J = 11.4 Hz, 1 H, CH), 4.06 (q, J = 7.2 Hz, 2 H, CH_2), 3.09 (d, J = 11.4 Hz, 1 H, CH), 1.67 (s, 3 H, CH_3), 1.01 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.30 (s, 3 F, CF_3) ppm. EI-MS (70 eV): m/z (%) = 230 (21) [M – 1 – $CF_3COCH_2CO_2Et]^+$, 121 (20) $[NO_2C_6H_4]^+$, 183 (14) $[CF_3COCHCO_2Et]^+$, 109 (33) [M – $CF_3COCH_2CO_2Et$ – $NO_2C_6H_4]^+$, 69 (100) $[CF_3]^+$, 43 (19) $[CH_3CO]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3346, 1730, 1600, 1523, 1349, 1172, 1025, 850, 747, 707, 410 cm^{-1}. $C_{17}H_{16}F_3N_3O_6$ (415.32): calcd. C 49.16, H 3.88, N 10.12; found: C 49.16, H 3.93, N 9.86.

Ethyl (4*S,5*R**)-4-(Furan-2-yl)-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4h):** This compound (237 mg, 66%) was obtained as a white solid with m.p. 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (s, 1 H, ArH), 6.34–6.25 (m, 2 H, ArH), 4.49 (d, J = 11.7 Hz, 1 H, CH), 4.11 (q, J = 7.2 Hz, 2 H, CH_2), 3.28 (d, J = 11.7 Hz, 1 H, CH), 2.18 (s, 6 H, CH_3COCH_3), 1.82 (s, 3 H, CH_3), 1.12 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.30 (s, 3 F, CF_3) ppm. EI-MS (70 eV): m/z (%) = 341 (1) [M – 1 – $H_2O]^+$, 176 (15) [M – $CF_3COCH_2CO_2Et]^+$, 69 (25) $[CF_3]^+$, 43 (100) $[CH_3CO]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3319, 2922, 1726, 1605, 1499, 1376, 1343, 1173, 1020, 729, 418 cm^{-1}. $C_{15}H_{15}F_3N_2O_5{\cdot}C_3H_6O$ (418.36): calcd. C 51.68, H 5.06, N 6.70; found: C 51.61, H 5.08, N 6.62.

Ethyl (4*S,5*R**)-4-(2-Fluorophenyl)-6-hydroxy-3-methyl-6-(trifluoromethyl)-2,4,5,6-tetrahydropyrazolo[3,4-*b*]pyran-5-carboxylate (4i):** This compound (184 mg, 50%) was obtained as a white solid with m.p. 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.02 (m, 5 H, ArH), 4.70 (d, J = 11.7 Hz, 1 H, CH), 4.01 (q, J = 7.2 Hz, 2 H, CH_2), 3.24 (d, J = 11.7 Hz, 1 H, CH), 1.69 (s, 3 H, CH_3), 1.00 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –83.49 (s, 3 F, CF_3), –119.61 (s, 1 F, ArF) ppm. EI-MS (70 eV): m/z (%) = 388 (1) $[M]^+$, 204 (47) [M – $CF_3COCH_2CO_2Et]^+$, 203 (46) [M – 1 – $CF_3COCH_2CO_2Et]^+$, 109 (73) [M – $CF_3COCH_2CO_2Et$ – $FC_6H_4]^+$, 69 (100) $[CF_3]^+$. IR (KBr): $\tilde{\nu}_{max}$ = 3349, 2986, 2936, 2730, 2529, 1727, 1606, 1523, 1491, 1341, 1237, 1159, 1090, 1020, 756, 705 cm^{-1}. $C_{17}H_{16}F_4N_2O_4$ (388.31): calcd. C 52.58, H 4.15, N 7.21; found: C 52.26, H 4.08, N 7.24.

X-ray Data for Compound 4h: $C_{18}H_2F_3N_2O_6$, FW = 418.37; orthorhombic; space group: $Pbca$, a = 15.7846(12), b = 14.0009(11), c = 18.0911(13) Å; α = 90.00°, β = 90.00°, γ = 90.00°; V = 3998.1(5) Å^3, Z = 8, D_c = 1.390 g cm^{-1}, F(000) = 1744. Radiation: Mo-K_α (λ = 0.71073 Å). Crystal dimension: 0.447 × 0.369 × 0.351 mm. Intensity data were collected at 293(2) K with a Bruker P4 four-circle diffractometer with graphite monochromator, and Mo-K_α radiation (λ = 0.71073 Å). A total of 5442 independent reflections were measured in the 2.25° < θ < 27.00° range. The structure was solved by directed methods and expanded by Fourier techniques. The non-hydrogen atoms were refined anisotropically; hydrogen atoms were included but not refined. The final cycle of full-matrix, least-square refinement was based on F^2. The final R and Rw value were 0.0419 and 0.0924, respectively. All calculations were performed with the program SHELX-97. CCDC-609828 contain(s) the supplementary crystallographic data for this paper (for **4h**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336033; or deposit@ccdc.cam.uk).

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