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A Stereoselective Three-Component Reaction:The Facile Synthesis of Fluorinated Tetrahydropyrimido[1,2-b]benzothiazoles

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A one-pot, catalyst- and solvent-free approach has been developed for the stereoselective synthesis of fluorinated tetrahydropyrimido[1,2-b]benzothiazoles. The three-component condensation reaction of an aldehyde and a trifluoromethyl *β*-dicarbonyl compound in the presence of 2-aminobenzothizole occurs in high yields at 90 ºC.

Keywords: Fluorinated compound, 2-Aminobenzothizole, 3-Amino-1,2,4-triazole, Solvent-free, Catalyst-free

INTRODUCTION

Recently, the synthesis of organofluorine compounds has received significant attention due to their biological activities [1-5]. Among these, heterocyclic compounds containing trifluoromethyl group are attractive targets for medicinal chemistry [6-8]. Some of the most well-known drugs are Prozac (anti-depressant), Diflucan (anti-fungal agent), Casodex (anti-cancer agent) and Desflurane (inhalation anesthetic) [9]. Mosher's acid and its derivatives are another important class of CF_3-containing compounds, which are widely used as chiral NMR resolution agents [10-12]. Therefore, the exploration of new effective methods for their synthesis is axiomatic.

Due to the atom economy, convergent character and simplicity of one-pot procedures, multi-component condensation reactions (*MCR*s) occupy a superior position compared with other reactions. Therefore, the discovery and development of novel *MCR*s is attracting growing interest from industrial chemistry research groups [13]. One of the first substrate classes involved in *MCR*s was the 1,3-dicarbonyl derivatives, which they used for the selective construction of highly functionalized small organic molecules with high synthetic and biological value [14,15]. However, a careful literature search reveals that the reaction of 2-aminobenzothiazol and aldehydes with ethyl 4,4,4-trifluoroacetoacetate under *MCR* strategy has not been studied.

In pursuit of our ongoing studies in the synthesis of new fluorinated organic compounds [16-18] and our growing interest in *MCR*s, Biginelli and Biginelli-like reactions [19-24], herein we wish to report the stereoselectively synthesis of fluorinated tetrahydropyrimido[1,2-b]benzothiazoles ring systems *via* the one-pot three-component condensation reaction of an aldehyde **1** and ethyl 4,4,4-trifluoroacetoacetate **2** in the presence of 2-aminobenzothiazol **3** under solvent-free conditions at 90 ºC without using any catalyst (Scheme 1).

EXPERIMENTAL

Apparatus

Melting points were measured on an Electrothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470

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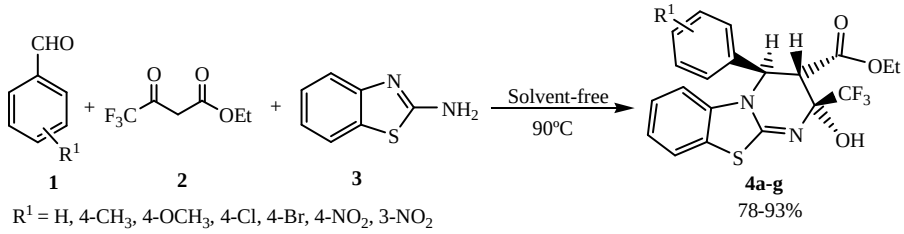


Scheme 1

spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX-300.13 AVANCE spectrometer at 300.13.13 and 75.47 MHz, respectively. NMR spectra were obtained on solutions in $CDCl_3$ and DMSO-d_6.

Typical Procedure for the Synthesis of Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(4-methylphenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-5-carboxylate (4a, $C_{21}H_{19}F_3N_2O_3S$)

A mixture of ethyl 4,4,4-trifluoroacetoacetate (0.184 g, 1 mmol), *para*-methylbenzaldehyde (0.120 g, 1 mmol), and 2-aminobenzthiazole (0.150 g, 1 mmol) was successively added to a screw-capped vial containing a magnetic stirring bar and was heated at 90 ºC in a preheated oil bath for 2 h. After completion of the reaction, the solid residue was crystallized from CH_2Cl_2/*n*-hexane 1:1 to yield 0.357 g of **4a** as a white powder (82%). m.p.: 161-163 ºC. IR (KBr, cm^{-1}): 3155, 1736, 1584, 1562, 1506. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.36 (s, 3H, $C_6H_4C\underline{H}_3$), 3.06 (d, J = 11.4 Hz, 1H, C<u>H</u>COOEt), 3.97-4.08 (m, 2H, $OC\underline{H}_2CH_3$), 4.64 (brs, 1H, O<u>H</u>), 5.36 (d, J = 11.4 Hz, 1H, C<u>H</u>-N), 6.14-7.30 (m, 8C<u>H</u> arom) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.63 ($OCH_2\underline{C}H_3$), 21.13 ($C_6H_4\underline{C}H_3$), 49.90 (<u>C</u>HCOOEt), 57.69 (<u>C</u>H-N), 61.91 ($O\underline{C}H_2CH_3$), 82.21 (q, $^{2}J_{CF}$ = 31.1 Hz, <u>C</u>-OH), 113.39 (<u>C</u> arom), 121.87 (<u>C</u> arom), 122.62 (<u>C</u> arom), 122.79 (<u>C</u> arom), 123.80 (q, $^{1}J_{CF}$ = 286.5 Hz, <u>C</u>F$_3$), 125.42 (<u>C</u> arom), 127.24 (<u>C</u> arom), 130.03 (<u>C</u> arom), 132.52 (<u>C</u> arom), 138.36 (<u>C</u> arom), 139.25 (<u>C</u> arom), 164.99 (<u>C</u>=N), 170.86 (<u>C</u>=O) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ -82 (s, 3F, CF_3) ppm. MS (EI, 70 eV): *m/z* (%) = 436 (M^+, 2), 286 (5), 217 (38), 150 (100), 69 (60). Anal. Calcd. for $C_{21}H_{19}F_3N_2O_3S$: C, 57.79; H, 4.39; N, 6.42; S, 7.35. Found: C, 56.92; H, 4.01; N, 6.27; S, 7.43.

Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(phenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-3-carboxylate (4b, $C_{20}H_{17}F_3N_2O_3S$). White powder (0.354 g, 84%): m.p.: 139-140 ºC. IR (KBr, cm^{-1}): 3070, 1739, 1584, 1561, 1462. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.05 (d, J = 11.4 Hz, 1H, C<u>H</u>COOEt), 3.97-4.05 (m, 2H, $OC\underline{H}_2CH_3$), 4.70 (brs, 1H, O<u>H</u>), 5.44 (d, J = 11.4 Hz, 1H, C<u>H</u>-N), 6.12-7.30 (m, 8C<u>H</u> arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.65 ($OCH_2\underline{C}H_3$), 49.99 (<u>C</u>HCOOEt), 57.99 (<u>C</u>H-N), 61.96 ($O\underline{C}H_2CH_3$), 82.10 (q, $^{2}J_{CF}$ = 31.0 Hz, <u>C</u>-OH), 113.46 (<u>C</u> arom), 121.98 (<u>C</u> arom), 122.68 (C arom), 123.06 (<u>C</u> arom), 124.50 (q, $^{1}J_{CF}$ = 283.5 Hz, <u>C</u>F$_3$), 125.54 (<u>C</u> arom), 127.42 (<u>C</u> arom), 129.38 (<u>C</u> arom), 129.41 (<u>C</u> arom), 135.54 (<u>C</u> arom), 138.16 (<u>C</u> arom), 165.16 (<u>C</u>=N), 170.42 (<u>C</u>=O). MS (EI, 70 eV): *m/z* (%) = 422 (M^+, 18), 353 (80), 272 (15), 246 (35), 177 (100), 150 (85), 69 (70). Anal. Calcd. for $C_{20}H_{17}F_3N_2O_3S$: C, 56.87; H, 4.06; N, 6.63; S, 7.59. Found: C, 56.48; H, 3.95; N, 6.72; S, 7.44.

Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(4-methoxy phenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzo-thiazole-5-carboxylate (4c, $C_{21}H_{19}F_3N_2O_4S$). White powder (0.342 g, 78%): m.p.: 146-148 ºC. IR (KBr, cm^{-1}): 3120, 1737, 1586, 1565, 1506. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.12 (d, J = 11.4 Hz, 1H, C<u>H</u>COOEt), 3.82 (s, 3H, $C_6H_4OC\underline{H}_3$), 3.99-4.08 (m, 2H, $OC\underline{H}_2CH_3$), 4.60 (brs, 1H, O<u>H</u>), 5.46 (d, J = 11.4 Hz, 1H, C<u>H</u>-N), 6.23-7.37 (m, 8C<u>H</u> arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.70 ($OCH_2\underline{C}H_3$), 50.00 (<u>C</u>HCOOEt), 55.35 (<u>C</u>H-N), 57.59 ($C_6H_4O\underline{C}H_3$), 62.00 ($O\underline{C}H_2CH_3$), 81.93 (q, $^{2}J_{CF}$ = 32.1 Hz, <u>C</u>-OH), 113.69 (<u>C</u> arom), 114.75 (<u>C</u> arom), 121.99 (<u>C</u> arom), 122.70 (<u>C</u> arom), 123.04 (<u>C</u> arom), 123.60 (q, $^{1}J_{CF}$ = 280.3 Hz, <u>C</u>F$_3$), 125.66 (<u>C</u> arom), 127.10 (<u>C</u> arom), 128.70 (<u>C</u> arom), 138.29 (<u>C</u> arom), 160.19 (<u>C</u> arom), 165.20 (<u>C</u>=N), 170.57 (<u>C</u>=O). MS (EI, 70

eV): *m/z* (%) = 452 (M^+, 2), 302 (5), 257 (30), 233 (50), 150 (50), 69 (100). Anal. Calcd. for $C_{21}H_{19}F_3N_2O_4S$: C, 55.75; H, 4.23; N, 6.19; S, 7.09. Found: C, 56.16; H, 4.12; N, 5.97; S, 7.34.

Ethyl-4-(Trifluoromethyl)-4-hydroxy-6-(4-bromophenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzo-thiazole-3-carboxylate (4d, $C_{20}H_{16}BrF_3N_2O_3S$). White powder (0.405 g, 81%): m.p.: 142-144 ºC. IR (KBr, cm^{-1}): 3230, 1732, 1592, 1580, 1483. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.00 (d, J = 11.3 Hz, 1H, C<u>H</u>COOEt), 3.99-4.05 (m, 2H, $OC\underline{H}_2CH_3$), 4.60 (brs, 1H, O<u>H</u>), 5.42 (d, J = 11.3 Hz, 1H, C<u>H</u>-N), 6.09-7.52 (m, 8C<u>H</u> arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.75 ($OCH_2\underline{C}H_3$), 49.86 (<u>C</u>HCOOEt), 57.19 (<u>C</u>H-N), 62.04 ($O\underline{C}H_2CH_3$), 82.23 (q, $^2J_{CF}$ = 31.1 Hz, <u>C</u>-OH), 113.11 (<u>C</u> arom), 121.74 (<u>C</u> arom), 122.53 (<u>C</u> arom), 123.09 (<u>C</u> arom), 123.30 (<u>C</u> arom), 125.58 (<u>C</u> arom), 129.05 (<u>C</u> arom), 130.16 (q, $^1J_{CF}$ = 289.00 Hz, <u>C</u>F_3), 132.59 (<u>C</u> arom), 134.93 (<u>C</u> arom), 137.94 (<u>C</u> arom), 164.86 (<u>C</u>=N), 169.99 (<u>C</u>=O). MS (EI, 70 eV): *m/z* (%) = 501 (M^+, 2), 433 (^{81}Br, 10), 431 (^{79}Br, 8), 352 (^{81}Br, 4), 350 (^{79}Br, 6), 307 (^{81}Br, 18), 305 (^{79}Br, 20), 283 (^{81}Br, 23), 281 (^{79}Br, 25), 150 (100), 69 (40). Anal. Calcd. for $C_{20}H_{16}BrF_3N_2O_3S$: C, 47.92; H, 3.22; N, 5.59; S, 6.40. Found: C, 47.63; H, 3.41; N, 5.66; S, 6.27.

Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(4-chlorophenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-3-carboxylate (4e, $C_{20}H_{16}ClF_3N_2O_3S$). White powder (0.426 g, 93%): m.p.: 138-139 ºC. IR (KBr, cm^{-1}): 3200, 1734, 1597, 1575, 1486. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, J = 6.96 Hz, 3H, $OCH_2C\underline{H}_3$), 3.01 (d, J = 11.3 Hz, 1H, C<u>H</u>COOEt), 3.96-4.07 (m, 2H, $OC\underline{H}_2CH_3$), 4.75 (brs, 1H, O<u>H</u>), 5.42 (d, J = 11.3 Hz, 1H, C<u>H</u>-N), 6.05-7.43 (m, 8C<u>H</u> arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.70 ($OCH_2\underline{C}H_3$), 49.86 (<u>C</u>HCOOEt), 57.14 (<u>C</u>H-N), 62.07 ($O\underline{C}H_2CH_3$), 82.20 (q, $^2J_{CF}$ = 31.2 Hz, <u>C</u>-OH), 113.12 (<u>C</u> arom), 122.05 (<u>C</u> arom), 122.57 (<u>C</u> arom), 123.08 (<u>C</u> arom), 124.15 (q, $^1J_{CF}$ = 290.5 Hz, <u>C</u>F_3), 125.57 (<u>C</u> arom), 128.77 (<u>C</u> arom), 129.65 (<u>C</u> arom), 134.35 (<u>C</u> arom), 135.20 (<u>C</u> arom), 137.95 (<u>C</u> arom), 164.88 (<u>C</u>=N), 170.14 (<u>C</u>=O). MS (EI, 70 eV): *m/z* (%) = 458 (M^+, 4), 389 (6), 306 (15), 150 (100), 69 (35). Anal. Calcd. for $C_{20}H_{16}ClF_3N_2O_3S$: C, 52.58; H, 3.53; N, 6.13; S, 7.02. Found: C, 53.22; H, 3.75; N, 5.98; S, 7.24.

Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(4-nitrophenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-3-carboxylate (4f, $C_{20}H_{16}F_3N_3O_5S$). Pale yellow powder (0.364 g, 78%): m.p.: 156-158 ºC. IR (KBr, cm^{-1}): 3105, 1737, 1585, 1570, 1518. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07 (t, J = 6.8 Hz, 3H, $OCH_2C\underline{H}_3$), 3.04 (d, J = 10.7 Hz, 1H, C<u>H</u>COOEt), 4.02-4.11 (m, 2H, $OC\underline{H}_2CH_3$), 5.59 (d, J = 10.7 Hz, 1H, C<u>H</u>-N), 6.02-8.26 (m, 8C<u>H</u> arom). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.02 ($OCH_2\underline{C}H_3$), 46.13 (<u>C</u>HCOOEt), 55.42 (<u>C</u>H-N), 61.41 ($O\underline{C}H_2CH_3$), 82.99 (q, $^2J_{CF}$ = 33.2 Hz, <u>C</u>-OH), 110.66 (<u>C</u> arom), 123.83 (<u>C</u> arom), 124.38 (<u>C</u> arom), 127.83 (q, $^1J_{CF}$ = 285.7 Hz, <u>C</u>F_3), 128.20 (<u>C</u>H arom), 138.37 (<u>C</u> arom), 139.53 (<u>C</u> arom), 144.35 (<u>C</u> arom), 146.56 (<u>C</u> arom), 147.06 (<u>C</u> arom), 148.01 (<u>C</u> arom), 162.56 (<u>C</u>=N), 168.84 (<u>C</u>=O). MS (EI, 70 eV): *m/z* (%) = 449 (M^+-H_2O, 2), 400 (5), 350 (10), 325 (20), 282 (100), 236 (60), 150 (70), 108 (68), 69 (55). Anal. Calcd. for $C_{20}H_{16}F_3N_3O_5S$: C, 51.39; H, 3.45; N, 8.99; S, 6.86. Found: C, 50.89; H, 3.36; N, 9.14; S, 6.52.

Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(3-nitrophenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-3-carboxylate (4g, $C_{20}H_{16}F_3N_3O_5S$). Pale yellow powder (0.420 g, 90%): m.p.: 175-177 ºC. IR (KBr, cm^{-1}): 3095, 1729, 1590, 1524, 1567. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13 (t, J = 6.9 Hz, 3H, $OCH_2C\underline{H}_3$), 3.37 (d, J = 10.7 Hz, 1H, C<u>H</u>COOEt), 4.03-4.09 (m, 2H, $OC\underline{H}_2CH_3$), 6.02 (d, J = 10.7 Hz, 1H, C<u>H</u>-N), 6.60-8.18 (m, 8C<u>H</u> arom). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.00 ($OCH_2\underline{C}H_3$), 46.20 (<u>C</u>HCOOEt), 55.23 (<u>C</u>H-N), 61.40 ($O\underline{C}H_2CH_3$), 83.31 (q, $^2J_{CF}$ = 30.2 Hz, <u>C</u>-OH), 110.60 (<u>C</u> arom), 121.82 (<u>C</u> arom), 121.96 (<u>C</u> arom), 122.79 (<u>C</u> arom), 123.17 (<u>C</u> arom), 123.63 (<u>C</u> arom), 124.31 (q, $^1J_{CF}$ = 280.3 Hz, <u>C</u>F_3), 127.04 (<u>C</u> arom), 130.15 (<u>C</u> arom), 133.74 (<u>C</u> arom), 139.48 (<u>C</u> arom), 141.20 (<u>C</u> arom), 148.20 (<u>C</u> arom), 162.76 (<u>C</u>=N), 168.94 (<u>C</u>=O). MS (EI, 70 eV): *m/z* (%) = 468 (MH^+, 8), 398 (25), 248 (80), 150 (95), 69 (100). Anal. Calcd. for $C_{20}H_{16}F_3N_3O_5S$: C, 51.39; H, 3.45; N, 8.99; S, 6.86. Found: C, 51.70; H, 3.56; N, 8.73; S, 6.54.

6-(Trifluoromethyl)-pyrimido[1,2-*b*]benzothiazole-4-one (6, $C_{11}H_6F_3N_3O$). White powder (0.215 g, 85%): m.p.: >280 ºC. IR (KBr, cm^{-1}): 3140, 1680, 1606, 1585, 1486. ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.45 (s, 1H, C<u>H</u>), 7.37-8.45 (m, 4C<u>H</u> arom). ^{13}C NMR (75 MHz, DMSO-d_6): δ 99.39 (<u>C</u>H), 111.88 (<u>C</u> arom), 116.34 (<u>C</u> arom), 121.71 (q, $^1J_{CF}$ = 274.1 Hz, <u>C</u>F_3), 122.86 (<u>C</u> arom), 125.96 (<u>C</u> arom), 127.28 (<u>C</u> arom), 130.86 (<u>C</u> arom), 150.37 (<u>C</u> arom), 151.31 (q, $^2J_{CF}$ = 33.8 Hz, <u>C</u>-CF_3), 159.42 (<u>C</u>=O). MS (EI, 70 eV): *m/z* (%) = 253 (M^+, 100), 225

(70) 206 (15), 184 (25), 156 (25), 133 (35), 90 (25), 69 (40). Anal. Calcd. for $C_{11}H_6F_3N_3O$: C, 52.18; H, 2.39; N, 16.60. Found: C, 51.94; H, 2.51; N, 17.02.

RESULT AND DISCUSSION

The reaction of an aldehyde with ethyl 4,4,4-trifluoroacetoacetate in the presence of 2-aminobenzothizole led to stereoselective formation of fluorinated tetrahydropyrimido[1,2-b]benzothiazoles **4a-g** in relatively high yields. The structures of the products were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ^{1}H NMR spectra of **4a** consisted of a triplet for the $\underline{CH_3}CH_2O$ group (δ = 1.01), a singlet for the $\underline{CH_3}C_6H_4$ (δ = 2.36), a doublet of doublet for the two $\underline{CH}$ groups (δ = 3.06 and 5.36 ppm, $^3J_{HH}$ = 11.4 Hz), and a multiplet for $CH_3\underline{CH_2}O$ (δ = 3.94-4.08). A broad signal for the OH group appeared at δ = 4.64 and a multiple for the aromatic hydrogen's appeared at δ = 6.14-7.30. The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 19 distinct resonances (two quartet at 82.21 ($^2J_{CF}$ = 31.12 Hz) for $\underline{C}$-OH and 123.80 ($^1J_{CF}$ = 286.50 Hz) for $\underline{CF_3}$ and also 17 signal for other carbons) in agreement with the suggested structure. The ^{1}H and ^{13}C NMR spectra of **4b-g** were similar to those of **4a** except for the R^1 group, which exhibited characteristic signals with appropriate chemical shifts.

To explore the scope and limitations of this reaction further, we extended our studies to the use of various *meta* and *para*-substituted benzaldehydes in the presence of 2-aminobenzothiazole. As indicated in Table 1, the reaction proceeded efficiently with both electron-withdrawing and electron-releasing *meta* and *para*-substituted benzaldehydes.

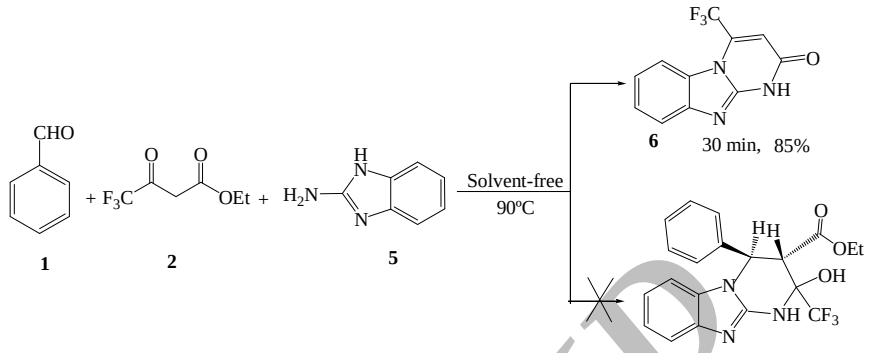
It is important to note that 2-aminobenzimidazole **5** react with fluorinate *β*-dicarbonyl compound (under the identical conditions) in a different manner, yielding 6-(trifluoromethyl)-pyrimido[1,2-b]benzothiazole-4-one **6** (Scheme 2). Formation of the latter evidently proceeds without the participation of the aldehyde component and is competitive with the three-component condensation reaction. Probably, this is a result of the higher nucleophilicity of the -NH_2 group of 2-aminobezimidazole as compared to 2-aminobenzothiazol. The high nucleophilicity of NH_2 group in 2-aminobenzimidazole in comparison to 2-aminobenzothiazol may be explained by the higher aromaticity of imidazole ring relative to thiazol ring. In other words, NH_2 group in 2-aminobezimidazole is less conjugated with imidazole ring relative to thiazol ring.

Compound **4a** has three stereogenic centers, and therefore four diastereomers are expected (Scheme 3). The ^{1}H NMR spectra of the crude reaction mixture obtained from **4a-g** showed a doublet of doublet at δ = 3.00-3.12 ppm and δ = 5.36-5.59 ppm ($^3J_{HH}$ = 10.66 to 11.44 Hz) for the H-5 and H-6 protons, respectively. These data were consistent with the presence of an anti-HCCH arrangement diastereomers (4R,5R, 6S or 4S,5R,6S and their mirror image geometries).

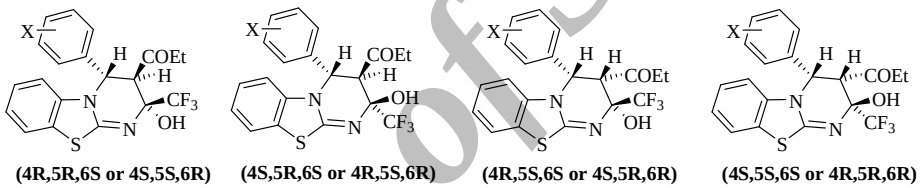
Crystal structure determination [25,26] of **4a** (Fig. 1)

Table 1. Synthesis of Fluorinated Tetrahydropyrimido[1,2-b]benzothiazoles

Entry	R^1	Product	Time (min)	Yield (%)
1	4-Me	**4a**	120	82
2	H	**4b**	60	84
3	4-OMe	**4c**	100	78
4	4-Cl	**4d**	60	81
5	4-Br	**4e**	45	93
6	4-NO_2	**4f**	35	78
7	3-NO_2	**4g**	15	90



Scheme 2



Scheme 3

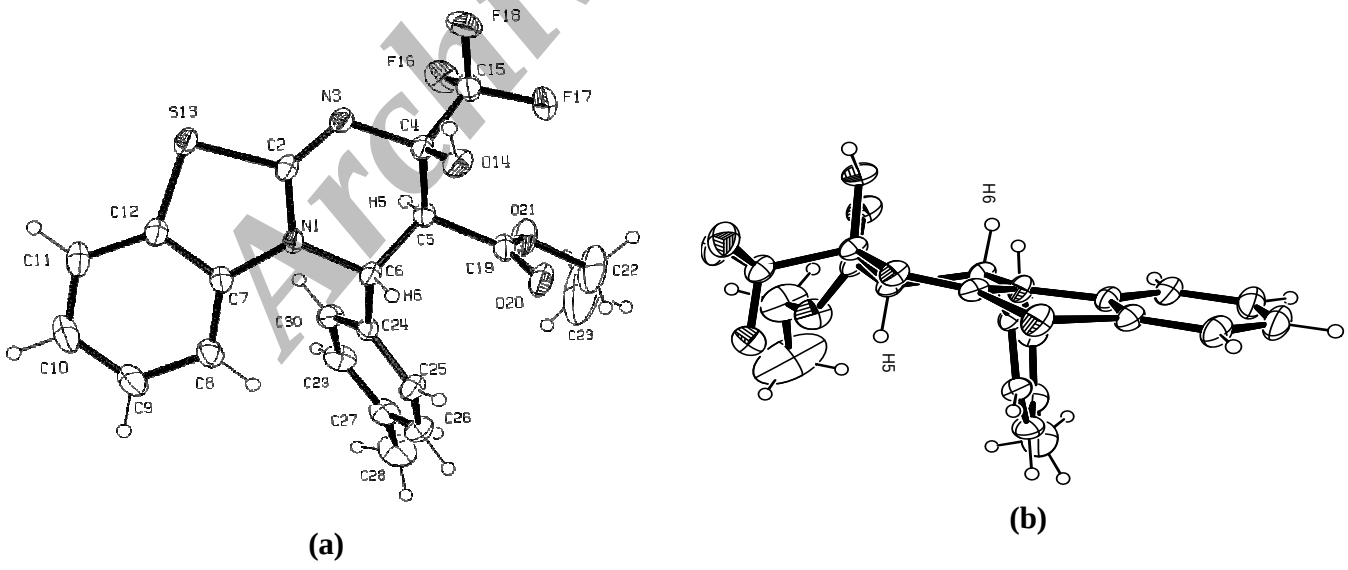
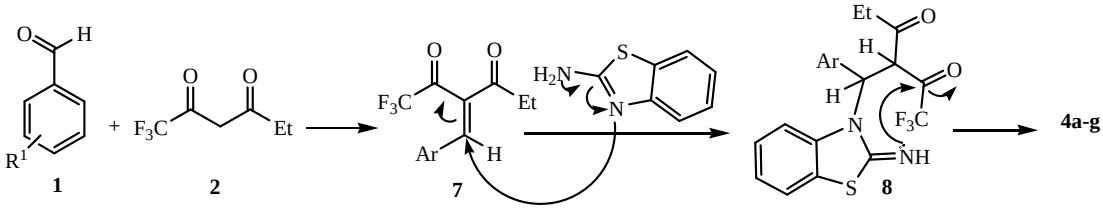


Fig. 1. (a): ORTEP representation of **4a**, (b): Side view of the compound that shows the anti configuration of the H5 and H6 hydrogens.



Scheme 4

clearly showed that vicinal OH-4 and COOEt groups are syn, and the **(4R,5S,6R)-4a** and its mirror image **(4S,5R,6S)-4a** is confirmed.

We have not established a mechanism for the formation of tetrahydropyrimido[1,2-b]benzothiazoles systems, but a reasonable possibility is indicated in Scheme 4. The reaction presumably proceeds in three steps: condensation of aldehyde **1** and ethyl 4,4,4-trifluoroacetoacetate **2** by a-standard *Knoevenagel* reaction to produce 3-benzylidene-2,4-pentanedione **7**, followed by a *Michael* addition of this product with 2-aminobenzothiazole **3** to give **8** which cyclizes to afford tetrahydropyrimido[1,2-b]benzothiazoles ring systems **4a-g** (Scheme 4).

In conclusion, we have introduced a novel stereoselective three-component condensation reaction leading to fluorinated tetrahydropyrimido[1,2-b]benzothiazoles systems in excellent yields from simple and readily available precursor under neutral conditions without using any catalyst or activator.

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