

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-aminobenzothiazole occurs in high yields at 90 °C.

Keywords: Fluorinated compound, 2-Aminobenzothiazole, 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 CF₃-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 (*MCRs*) occupy a superior position compared with other reactions. Therefore, the discovery and development of novel *MCRs* is attracting growing interest from industrial chemistry research groups [13]. One of the first substrate classes involved in *MCRs* 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-aminobenzothiazole and aldehydes with ethyl 4,4,4-trifluoroacetoacetate under *MCR* strategy has not been studied.

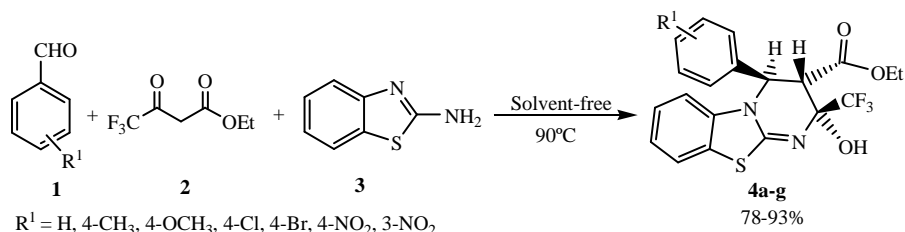
In pursuit of our ongoing studies in the synthesis of new fluorinated organic compounds [16-18] and our growing interest in *MCRs*, Biginelli and Biginelli-like reactions [19-24], herein we wish to report the stereoselective synthesis of fluorinated tetrahydropyrimido[1,2-b]benzothiazoles ring systems *via* the one-pot three-component condensation reaction of an aldehyde **1** and ethyl 4,4,4-trifluoroacetoacetate **2** in the presence of 2-aminobenzothiazole **3** under solvent-free conditions at 90 °C 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. ^1H 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 $\text{DMSO-}d_6$.

Typical Procedure for the Synthesis of Ethyl-4-(trifluoromethyl)-4-hydroxy-6-(4-methylphenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-3-carboxylate (4a, $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{S}$)

A mixture of ethyl 4,4,4-trifluoroacetate (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 °C in a preheated oil bath for 2 h. After completion of the reaction, the solid residue was crystallized from $\text{CH}_2\text{Cl}_2/n$ -hexane 1:1 to yield 0.357 g of **4a** as a white powder (82%). m.p.: 161-163 °C. IR (KBr, cm^{-1}): 3155, 1736, 1584, 1562, 1506. ^1H NMR (300 MHz, CDCl_3): δ 1.01 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.36 (s, 3H, $\text{C}_6\text{H}_4\text{CH}_3$), 3.06 (d, $J = 11.4$ Hz, 1H, CHCOOEt), 3.97-4.08 (m, 2H, OCH_2CH_3), 4.64 (brs, 1H, OH), 5.36 (d, $J = 11.4$ Hz, 1H, CH-N), 6.14-7.30 (m, 8CH arom) ppm. ^{13}C NMR (75 MHz, CDCl_3): δ 13.63 (OCH_2CH_3), 21.13 ($\text{C}_6\text{H}_4\text{CH}_3$), 49.90 (CHCOOEt), 57.69 (CH-N), 61.91 (OCH_2CH_3), 82.21 (q, $^2J_{\text{CF}} = 31.1$ Hz, C-OH), 113.39 (C arom), 121.87 (C arom), 122.62 (C arom), 122.79 (C arom), 123.80 (q, $^1J_{\text{CF}} = 286.5$ Hz, CF_3), 125.42 (C arom), 127.24 (C arom), 130.03 (C arom), 132.52 (C arom), 138.36 (C arom), 139.25 (C arom), 164.99 (C=N), 170.86 (C=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 $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_3\text{S}$: 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**, $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{S}$). White powder (0.354 g, 84%): m.p.: 139-140 °C. IR (KBr, cm^{-1}): 3070, 1739, 1584, 1561, 1462. ^1H NMR (300 MHz, CDCl_3): δ 0.99 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.05 (d, $J = 11.4$ Hz, 1H, CHCOOEt), 3.97-4.05 (m, 2H, OCH_2CH_3), 4.70 (brs, 1H, OH), 5.44 (d, $J = 11.4$ Hz, 1H, CH-N), 6.12-7.30 (m, 8CH arom). ^{13}C NMR (75 MHz, CDCl_3): δ 13.65 (OCH_2CH_3), 49.99 (CHCOOEt), 57.99 (CH-N), 61.96 (OCH_2CH_3), 82.10 (q, $^2J_{\text{CF}} = 31.0$ Hz, C-OH), 113.46 (C arom), 121.98 (C arom), 122.68 (C arom), 123.06 (C arom), 124.50 (q, $^1J_{\text{CF}} = 283.5$ Hz, CF_3), 125.54 (C arom), 127.42 (C arom), 129.38 (C arom), 129.41 (C arom), 135.54 (C arom), 138.16 (C arom), 165.16 (C=N), 170.42 (C=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 $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3\text{S}$: 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-methoxyphenyl)-1,4,5,6-tetrahydropyrimido[1,2-b]benzothiazole-3-carboxylate (4c, $\text{C}_{21}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4\text{S}$)

White powder (0.342 g, 78%): m.p.: 146-148 °C. IR (KBr, cm^{-1}): 3120, 1737, 1586, 1565, 1506. ^1H NMR (300 MHz, CDCl_3): δ 1.04 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.12 (d, $J = 11.4$ Hz, 1H, CHCOOEt), 3.82 (s, 3H, $\text{C}_6\text{H}_4\text{OCH}_3$), 3.99-4.08 (m, 2H, OCH_2CH_3), 4.60 (brs, 1H, OH), 5.46 (d, $J = 11.4$ Hz, 1H, CH-N), 6.23-7.37 (m, 8CH arom). ^{13}C NMR (75 MHz, CDCl_3): δ 13.70 (OCH_2CH_3), 50.00 (CHCOOEt), 55.35 (CH-N), 57.59 ($\text{C}_6\text{H}_4\text{OCH}_3$), 62.00 (OCH_2CH_3), 81.93 (q, $^2J_{\text{CF}} = 32.1$ Hz, C-OH), 113.69 (C arom), 114.75 (C arom), 121.99 (C arom), 122.70 (C arom), 123.04 (C arom), 123.60 (q, $^1J_{\text{CF}} = 280.3$ Hz, CF_3), 125.66 (C arom), 127.10 (C arom), 128.70 (C arom), 138.29 (C arom), 160.19 (C arom), 165.20 (C=N), 170.57 (C=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 °C. IR (KBr, cm^{-1}): 3230, 1732, 1592, 1580, 1483. 1H NMR (300 MHz, $CDCl_3$): δ 1.06 (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 3.00 (d, $J = 11.3$ Hz, 1H, $CHCOOEt$), 3.99-4.05 (m, 2H, OCH_2CH_3), 4.60 (brs, 1H, OH), 5.42 (d, $J = 11.3$ Hz, 1H, $CH-N$), 6.09-7.52 (m, 8CH arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.75 (OCH_2CH_3), 49.86 ($CHCOOEt$), 57.19 ($CH-N$), 62.04 (OCH_2CH_3), 82.23 (q, $^2J_{CF} = 31.1$ Hz, $C-OH$), 113.11 (C arom), 121.74 (C arom), 122.53 (C arom), 123.09 (C arom), 123.30 (C arom), 125.58 (C arom), 129.05 (C arom), 130.16 (q, $^1J_{CF} = 289.00$ Hz, CF_3), 132.59 (C arom), 134.93 (C arom), 137.94 (C arom), 164.86 ($C=N$), 169.99 ($C=O$). 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 °C. IR (KBr, cm^{-1}): 3200, 1734, 1597, 1575, 1486. 1H NMR (300 MHz, $CDCl_3$): δ 1.05 (t, $J = 6.96$ Hz, 3H, OCH_2CH_3), 3.01 (d, $J = 11.3$ Hz, 1H, $CHCOOEt$), 3.96-4.07 (m, 2H, OCH_2CH_3), 4.75 (brs, 1H, OH), 5.42 (d, $J = 11.3$ Hz, 1H, $CH-N$), 6.05-7.43 (m, 8CH arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.70 (OCH_2CH_3), 49.86 ($CHCOOEt$), 57.14 ($CH-N$), 62.07 (OCH_2CH_3), 82.20 (q, $^2J_{CF} = 31.2$ Hz, $C-OH$), 113.12 (C arom), 122.05 (C arom), 122.57 (C arom), 123.08 (C arom), 124.15 (q, $^1J_{CF} = 290.5$ Hz, CF_3), 125.57 (C arom), 128.77 (C arom), 129.65 (C arom), 134.35 (C arom), 135.20 (C arom), 137.95 (C arom), 164.88 ($C=N$), 170.14 ($C=O$). 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-carbo-

xylate (4f, $C_{20}H_{16}F_3N_3O_3S$). Pale yellow powder (0.364 g, 78%): m.p.: 156-158 °C. IR (KBr, cm^{-1}): 3105, 1737, 1585, 1570, 1518. 1H NMR (300 MHz, $DMSO-d_6$): δ 1.07 (t, $J = 6.8$ Hz, 3H, OCH_2CH_3), 3.04 (d, $J = 10.7$ Hz, 1H, $CHCOOEt$), 4.02-4.11 (m, 2H, OCH_2CH_3), 5.59 (d, $J = 10.7$ Hz, 1H, $CH-N$), 6.02-8.26 (m, 8CH arom). ^{13}C NMR (75 MHz, $DMSO-d_6$): δ 14.02 (OCH_2CH_3), 46.13 ($CHCOOEt$), 55.42 ($CH-N$), 61.41 (OCH_2CH_3), 82.99 (q, $^2J_{CF} = 33.2$ Hz, $C-OH$), 110.66 (C arom), 123.83 (C arom), 124.38 (C arom), 127.83 (q, $^1J_{CF} = 285.7$ Hz, CF_3), 128.20 (CH arom), 138.37 (C arom), 139.53 (C arom), 144.35 (C arom), 146.56 (C arom), 147.06 (C arom), 148.01 (C arom), 162.56 ($C=N$), 168.84 ($C=O$). 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 $C_{20}H_{16}F_3N_3O_3S$: 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, $C_{20}H_{16}F_3N_3O_3S$). Pale yellow powder (0.420 g, 90%): m.p.: 175-177 °C. IR (KBr, cm^{-1}): 3095, 1729, 1590, 1524, 1567. 1H NMR (300 MHz, $DMSO-d_6$): δ 1.13 (t, $J = 6.9$ Hz, 3H, OCH_2CH_3), 3.37 (d, $J = 10.7$ Hz, 1H, $CHCOOEt$), 4.03-4.09 (m, 2H, OCH_2CH_3), 6.02 (d, $J = 10.7$ Hz, 1H, $CH-N$), 6.60-8.18 (m, 8CH arom). ^{13}C NMR (75 MHz, $DMSO-d_6$): δ 14.00 (OCH_2CH_3), 46.20 ($CHCOOEt$), 55.23 ($CH-N$), 61.40 (OCH_2CH_3), 83.31 (q, $^2J_{CF} = 30.2$ Hz, $C-OH$), 110.60 (C arom), 121.82 (C arom), 121.96 (C arom), 122.79 (C arom), 123.17 (C arom), 123.63 (C arom), 124.31 (q, $^1J_{CF} = 280.3$ Hz, CF_3), 127.04 (C arom), 130.15 (C arom), 133.74 (C arom), 139.48 (C arom), 141.20 (C arom), 148.20 (C arom), 162.76 ($C=N$), 168.94 ($C=O$). MS (EI, 70 eV): m/z (%) = 468 (MH^+ , 8), 398 (25), 248 (80), 150 (95), 69 (100). Anal. Calcd. for $C_{20}H_{16}F_3N_3O_3S$: 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 °C. IR (KBr, cm^{-1}): 3140, 1680, 1606, 1585, 1486. 1H NMR (300 MHz, $DMSO-d_6$): δ 6.45 (s, 1H, CH), 7.37-8.45 (m, 4CH arom). ^{13}C NMR (75 MHz, $DMSO-d_6$): δ 99.39 (CH), 111.88 (C arom), 116.34 (C arom), 121.71 (q, $^1J_{CF} = 274.1$ Hz, CF_3), 122.86 (C arom), 125.96 (C arom), 127.28 (C arom), 130.86 (C arom), 150.37 (C arom), 151.31 (q, $^2J_{CF} = 33.8$ Hz, $C-CF_3$), 159.42 ($C=O$). 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 C₁₁H₆F₃N₃O: 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-aminobenzothiazole 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, ¹H NMR and ¹³C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m/z* values. The ¹H NMR spectra of **4a** consisted of a triplet for the CH₃CH₂O group ($\delta = 1.01$), a singlet for the CH₃C₆H₄ ($\delta = 2.36$), a doublet of doublet for the two CH groups ($\delta = 3.06$ and 5.36 ppm, $^3J_{\text{HH}} = 11.4$ Hz), and a multiplet for CH₃CH₂O ($\delta = 3.94$ - 4.08). A broad signal for the OH group appeared at $\delta = 4.64$ and a multiple for the aromatic hydrogen's appeared at $\delta = 6.14$ - 7.30 . The ¹H decoupled ¹³C NMR spectrum of **4a** showed 19 distinct resonances (two quartet at 82.21 ($^2J_{\text{CF}} = 31.12$ Hz) for C-OH and 123.80 ($^1J_{\text{CF}} = 286.50$ Hz) for CF₃ and also 17 signal for other carbons) in agreement with the suggested structure. The ¹H and ¹³C NMR spectra of **4b-g** were similar to those of **4a** except for the R¹ 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 -NH₂ group of 2-aminobenzimidazole as compared to 2-aminobenzothiazol. The high nucleophilicity of NH₂ 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, NH₂ group in 2-aminobenzimidazole is less conjugated with imidazole ring relative to thiazol ring.

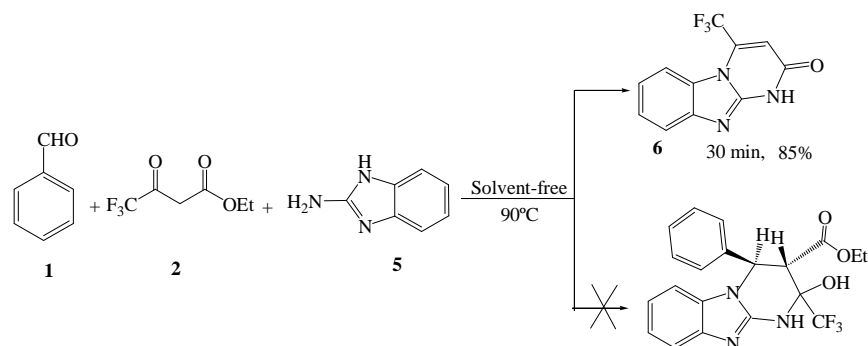
Compound **4a** has three stereogenic centers, and therefore four diastereomers are expected (Scheme 3). The ¹H NMR spectra of the crude reaction mixture obtained from **4a-g** showed a doublet of doublet at $\delta = 3.00$ - 3.12 ppm and $\delta = 5.36$ - 5.59 ppm ($^3J_{\text{HH}} = 10.66$ to 11.44 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)

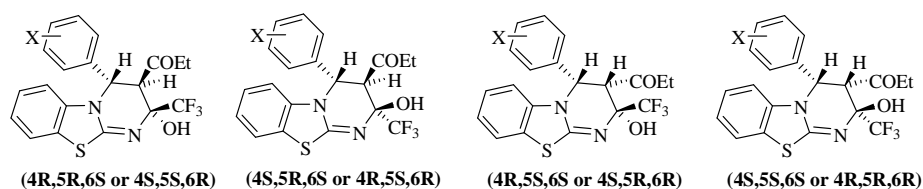
Table 1. Synthesis of Fluorinated Tetrahydropyrimido[1,2-b]benzothiazoles

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

A Stereoselective Three-Component Reaction



Scheme 2



Scheme 3

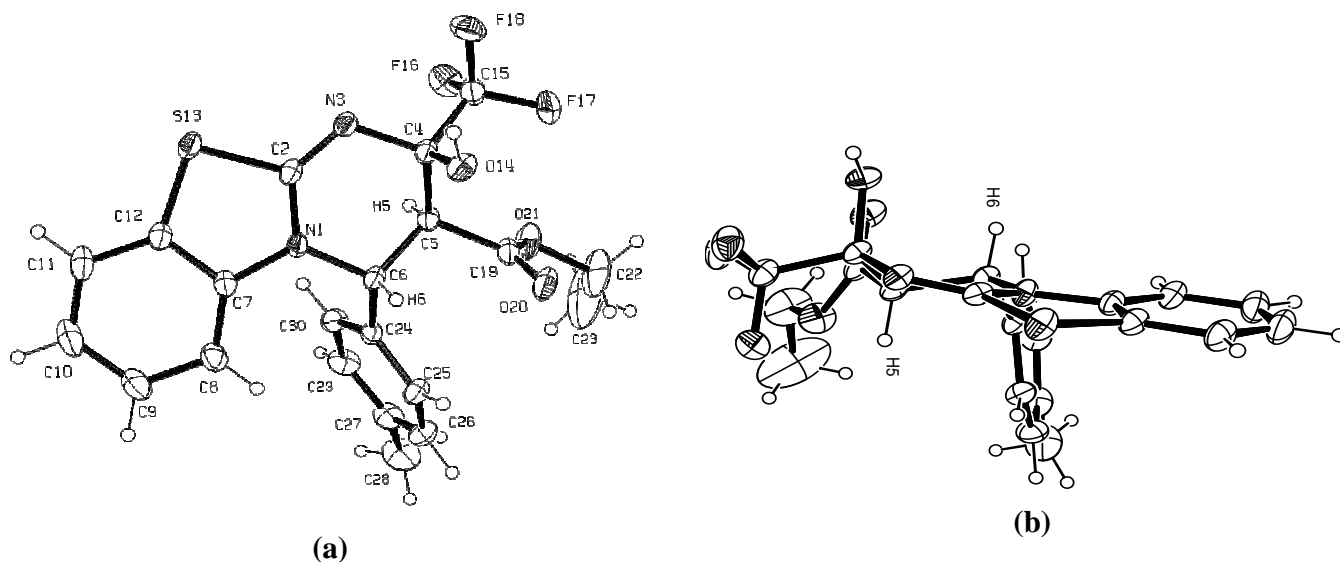
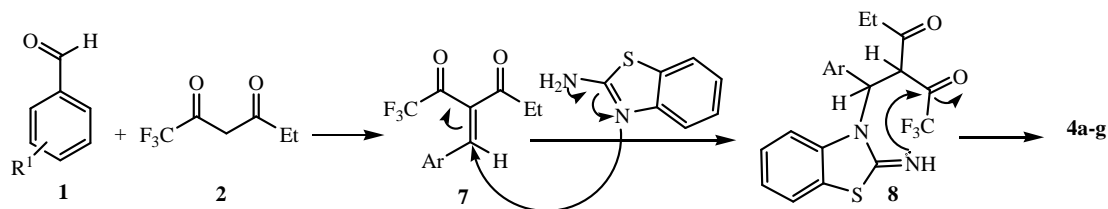


Fig. 1. (a): ORTEP representation of **4a**, (b): Side view of the compound that shows the anti configuration of the H5 and H6 hydrogens.



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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