J. Iran. Chem. Soc., Vol. 8, No. 1, March 2011, pp. 24-30.

JOURNAL OF THE Iranian Chemical Society

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

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(Received 2 October 2008, Accepted 10 December 2009)

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 °C.

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 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 2aminobenzothiazol and aldehydes with ethyl 4,4,4trifluoroacetoacetate 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 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 °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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spectrometer. ¹H and ¹³C 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-5carboxylate (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 2aminobenzthiazole (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 CH₂Cl₂/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, CDCl₃): δ 1.01 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 2.36 (s, 3H, C₆H₄CH₃), 3.06 (d, J =11.4 Hz, 1H, CHCOOEt), 3.97-4.08 (m, 2H, OCH2CH3), 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. ¹³C NMR (75 MHz, CDCl₃): δ 13.63 (OCH₂<u>C</u>H₃), 21.13 (C₆H₄<u>C</u>H₃), 49.90 (<u>C</u>HCOOEt), 57.69 (<u>C</u>H-N), 61.91 (O<u>C</u>H₂CH₃), 82.21 (q, ${}^{2}J_{CF} = 31.1$ Hz, <u>C</u>-OH), 113.39 (C arom), 121.87 (C arom), 122.62 (C arom), 122.79 (<u>C</u> arom), 123.80 (q, ${}^{1}J_{CF} = 286.5$ Hz, <u>CF₃</u>), 125.42 (<u>C</u> arom), 127.24 (C arom), 130.03 (C arom), 132.52 (C 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. ¹⁹F NMR (282 MHz, CDCl₃): δ -82 (s, 3F, CF₃) ppm. MS (EI, 70 eV): m/z (%) = 436 (M⁺, 2), 286 (5), 217 (38), 150 (100), 69 (60). Anal. Calcd. for C₂₁H₁₉F₃N₂O₃S: 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)-1,4,5,6tetrahydropyrimido[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 °C. IR (KBr, cm⁻¹): 3070, 1739, 1584, 1561, 1462. ¹H NMR (300 MHz, CDCl₃): δ 0.99 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 3.05 (d, J = 11.4 Hz, 1H, CHCOOEt), 3.97-4.05 (m, 2H, OCH₂CH₃), 4.70 (brs, 1H, OH), 5.44 (d, J = 11.4 Hz, 1H, CH-N), 6.12-7.30 (m, 8CH arom). ¹³C NMR (75 MHz, CDCl₃): δ 13.65 (OCH₂<u>C</u>H₃), 49.99 (<u>C</u>HCOOEt), 57.99 (<u>C</u>H-N), 61.96 (O<u>C</u>H₂CH₃), 82.10 (q, ${}^{2}J_{CF} = 31.0$ Hz, <u>C</u>-OH), 113.46 (C arom), 121.98 (C arom), 122.68 (C arom), 123.06 (<u>C</u> arom), 124.50 (q, ${}^{1}J_{CF}$ = 283.5 Hz, <u>C</u>F₃), 125.54 (<u>C</u> arom), 127.42 (C arom), 129.38 (C arom), 129.41 (C 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 C₂₀H₁₇F₃N₂O₃S: 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, C₂₁H₁₉F₃N₂O₄S). White powder (0.342 g, 78%): m.p.: 146-148 °C. IR (KBr, cm⁻¹): 3120, 1737, 1586, 1565, 1506. ¹H NMR (300 MHz, CDCl₃): δ 1.04 (t, *J* = 7.1 Hz, 3H, OCH₂C<u>H₃</u>), 3.12 (d, *J* = 11.4 Hz, 1H, C<u>H</u>COOEt), 3.82 (s, 3H, C₆H₄OC<u>H₃</u>), 3.99-4.08 (m, 2H, OC<u>H</u>₂CH₃), 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). ¹³C NMR (75 MHz, CDCl₃): δ 13.70 (OCH₂C<u>H₃</u>), 50.00 (<u>C</u>HCOOEt), 55.35 (<u>C</u>H-N), 57.59 (C₆H₄O<u>C</u>H₃), 62.00 (O<u>C</u>H₂CH₃), 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>F₃), 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 C₂₁H₁₉F₃N₂O₄S: 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, C₂₀H₁₆BrF₃N₂O₃S). White powder (0.405 g, 81%): m.p.: 142-144 °C. IR (KBr, cm⁻¹): 3230, 1732, 1592, 1580, 1483. ¹H NMR (300 MHz, CDCl₃): δ 1.06 (t, J = 7.1 Hz, 3H, OCH₂CH₃), 3.00 (d, J = 11.3 Hz, 1H, CHCOOEt), 3.99-4.05 (m, 2H, OCH₂CH₃), 4.60 (brs, 1H, OH), 5.42 (d, J = 11.3 Hz, 1H, CH-N), 6.09-7.52 (m, 8CH arom). ¹³C NMR (75 MHz, CDCl₃): δ 13.75 (OCH₂CH₃), 49.86 (CHCOOEt), 57.19 (<u>C</u>H-N), 62.04 (O<u>C</u>H₂CH₃), 82.23 (q, ${}^{2}J_{CF}$ = 31.1 Hz, <u>C</u>-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, ${}^{1}J_{CF} = 289.00$ Hz, CF₃), 132.59 (C arom), 134.93 (C arom), 137.94 (C arom), 164.86 (C=N), 169.99 (<u>C</u>=O). MS (EI, 70 eV): m/z (%) = 501 (M⁺, 2), 433 (⁸¹Br, 10), 431 (⁷⁹Br, 8), 352 (⁸¹Br, 4), 350 (⁷⁹Br, 6), 307 (⁸¹Br, 18), 305 (⁷⁹Br, 20), 283 (⁸¹Br, 23), 281 (⁷⁹Br, 25), 150 (100), 69 (40). Anal. Calcd. for C₂₀H₁₆BrF₃N₂O₃S: 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-3carboxylate (4e, C₂₀H₁₆ClF₃N₂O₃S). White powder (0.426 g, 93%): m.p.: 138-139 °C. IR (KBr, cm⁻¹): 3200, 1734, 1597, 1575, 1486. ¹H NMR (300 MHz, CDCl₃): δ 1.05 (t, J = 6.96Hz, 3H, OCH_2CH_3), 3.01 (d, J = 11.3 Hz, 1H, CHCOOEt), 3.96-4.07 (m, 2H, OCH₂CH₃), 4.75 (brs, 1H, OH), 5.42 (d, J =11.3 Hz, 1H, CH-N), 6.05-7.43 (m, 8CH arom). ¹³C NMR (75 MHz, CDCl₃): δ 13.70 (OCH₂CH₃), 49.86 (CHCOOEt), 57.14 (<u>C</u>H-N), 62.07 (O<u>C</u>H₂CH₃), 82.20 (q, ${}^{2}J_{CF}$ = 31.2 Hz, <u>C</u>-OH), 113.12 (C arom), 122.05 (C arom), 122.57 (C arom), 123.08 (<u>C</u> arom), 124.15 (q, ${}^{1}J_{CF}$ = 290.5 Hz, <u>C</u>F₃), 125.57 (<u>C</u> arom), 128.77 (C arom), 129.65 (C arom), 134.35 (C 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 C₂₀H₁₆ClF₃N₂O₃S: 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, C₂₀H₁₆F₃N₃O₅S). 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 = 6.8Hz, 3H, OCH₂CH₃), 3.04 (d, J = 10.7 Hz, 1H, CHCOOEt), 4.02-4.11 (m, 2H, OCH₂CH₃), 5.59 (d, J = 10.7 Hz, 1H, CH-N), 6.02-8.26 (m, 8C<u>H</u> arom). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 14.02 (OCH₂<u>C</u>H₃), 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, ${}^{I}J_{CF} =$ 285.7 Hz, CF₃), 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⁺-H₂O, 2), 400 (5), 350 (10), 325 (20), 282 (100), 236 (60), 150 (70), 108 (68), 69 (55). Anal. Calcd. for C₂₀H₁₆F₃N₃O₅S: 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, C₂₀H₁₆F₃N₃O₅S). 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 = 6.9Hz, 3H, OCH₂CH₃), 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_2 -N), 6.60-8.18 (m, 8C<u>H</u> arom). ¹³C NMR (75 MHz, DMSO-*d*₆): δ 14.00 (OCH₂<u>C</u>H₃), 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 (C arom), 121.96 (C arom), 122.79 (C arom), 123.17 (<u>C</u> arom), 123.63 (<u>C</u> arom), 124.31 (q, ${}^{1}J_{CF} = 280.3$ Hz, <u>CF₃</u>), 127.04 (<u>C</u> arom), 130.15 (<u>C</u> arom), 133.74 (<u>C</u> arom), 139.48 (C arom), 141.20 (C arom), 148.20 (C 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 C₂₀H₁₆F₃N₃O₅S: 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, C₁₁H₆F₃N₃O). 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): \delta 6.45 (s, 1H, C<u>H</u>), 7.37-8.45 (m, 4C<u>H</u> arom). ¹³C NMR (75 MHz, DMSO-***d***₆): \delta 99.39 (<u>C</u>H), 111.88 (<u>C</u> arom), 116.34 (<u>C</u> arom), 121.71 (q, ¹***J***_{CF} = 274.1 Hz, <u>C</u>F₃), 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, ²***J***_{CF} = 33.8 Hz, <u>C</u>-CF₃), 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 4,4,4trifluoroacetoacetate 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, 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 <u>CH</u>₃CH₂O group ($\delta = 1.01$), a singlet for the $CH_3C_6H_4$ ($\delta = 2.36$), a doublet of doublet for the two CH groups ($\delta = 3.06$ and 5.36 ppm, ${}^{3}J_{HH} = 11.4$ Hz), and a multiplet for CH₃CH₂O (δ = 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 (${}^{2}J_{CF} = 31.12$ Hz) for C-OH and 123.80 (${}^{1}J_{CF} =$ 286.50 Hz) for CF_3 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 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 threecomponent condensation reaction. Probably, this is a result of the higher nucleophilicity of the -NH₂ group of 2aminobezimidazole 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-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 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_{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)

Entry	\mathbf{R}^1	Product	Time (min)	Yield (%)
1	4-Me	4 a	120	82
2	Н	4b	60	84
3	4-OMe	4 c	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	4 g	15	90

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

A Stereoselective Three-Component Reaction



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

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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.

ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University.

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