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A Convenient Synthesis of Ethyl 1-Amino-3-(Substituted Phenyl)-2-Cyano-3*H*-Benzo[4,5]Thiazolo-[3,2-*a*] Pyridine-4-Carboxylate Derivatives and Some of their Reactions

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Abstract The titled compounds were prepared by interaction of ethyl 2-(benzo[*d*]thazol-2-yl)acetate **(3)** with different arylidinemalononitrile derivatives **(4a-c)** in EtOH/TEA solution at room temperature. When **3** was treated with 2-(ethoxymethylene)-malononitrile **(4f)** under same reaction conditions, the ethyl iminothiazolopyridine-4-carboxylate **(6)** was obtained. Ethyl (amino(methoxy)methyl)-3-(substitutedphenyl)-1-oxo-1*H*-benzo[4,5]thiazole[3,2-*a*]pyridine-4-carboxylate **(8a,b)** was obtained from reaction of **3** with different cyanoacrylate derivatives **(7a,b)** in MeOH/TEA at room temperature, while the diethyl thiazolo[3,2-*a*]pyridine-4-carboxylate derivative **(8c)** was obtained under same reaction conditions. The amino-imino derivative **(10)** was also prepared and used to synthesis new pyrido[3,2-*e*][1,2,4]triaziolo[1,5-*c*]pyrimidine-5-carboxylate derivatives **(12)**. The structures of all the newly synthesized compounds were confirmed based on their elemental analysis and spectroscopic data.

Keywords: *ethyl 2-(benzo[d]thazol-2-yl)acetate, arylidinemalononitrile, pyridine-4-carboxylate, triaziolo[1,5-c]pyrimidine-5-carboxylate*

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1. Introduction

The twentieth century has been characterized both by a drastic reduction in the mortality caused by infectious diseases and by a rise in the control of neoplastic pathologies. Nevertheless, microorganism and viruses, on the one hand, and tumors, on the other hand, still represent a dreadful menace to men's health and therefore, for a more efficient control, require the steady development of novel and more powerful drugs.

Benzothiazole derivatives possess a wide spectrum of biological applications such as antitumor [1,2,3,4], antimicrobial [5,6,7,8], schictosomicidal [9], anti-inflammatory [10,11,12,13], anticonvulsants [14,15], antidiabetic [16,17], antipsychotic [18] and diuretic [19]. Due to these biological activities, the synthesis of benzothiazole is a considerable area of current discussion. The classical method involves condensation of *o*-aminothiophenols with substituted aldehydes [20,21], acyl chlorides, carboxylic acids [22,23] or esters, nitriles [24]. Other most commonly used methods include Pd/Cu/Mn/chloranil catalyzed cyclization of *o*-halothioformanilides [25,26]. To this end, as a continuation of a research program on synthesis of heterocyclic compounds with potential biological activity [27-34], I decided to study the synthetic potentiality of ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** **[35]** towards some reagents as a convenient route to condensed and substituted benzothiazole.

2. Experimental

2.1. Chemicals and Instruments

Melting points were determined on a Stuart melting point apparatus and are uncorrected. IR spectrawere recorded in KBr using a FT-IR 5300 spectrometer and Perkin Elmer spectrum RXIFT-IR system (ν, cm^{-1}). The ^{1}H NMR at (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in DMSO-$d_6$on a Varian Mercury VX-300 NMR spectrometer. Chemical shifts (δ) are related to that of thesolvent. Mass spectra were measured on a Shimadzu GMMS-QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Microanalytical Center, Cairo University, Cairo (Egypt).

2.2. Starting Materials

Ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** was prepared according to previously reported procedures [35]. All

other chemicals used inthis study were commercially available.

2.3. Typical Procedure for Synthesis of (5a-e)

A Solution of ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** (2.21 g, 10 mmol) in ethanol was added to mixture of ethanolic solution of the appropriate arylidinemalononitrile **(4a-e)** (10 mmol) and triethyl amine (TEA). The mixture was stirred at room temperature for 3-4 hr. until complete precipitation. The solid formed was filtered off, washed by ethanol and recrystalized from ethanol-benzene mixture (1:1) to give compound **5**.

2.3.1. Ethyl 1-amino-2-cyano-3-phenyl-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate (5a)

Yellow; Mp 210-212°C; FTIR (KBr, cm^{-1}): 3430, 3337 (NH_2), 2186 (CN), 1668 (CO-ester). ^1H NMR (DMSO-d_6, 300 MHz): 1.20 (t, 3H, $\underline{CH_3}CH_2$), 4.11-4.17 (q, 2H, $CH_3\underline{CH_2}$), 4.16 (s, 1H, 3H-pyridine), 6.49 (brs, 2H, NH_2; cancelled by D_2O), 7.15-7.38 (m, 7H, Ar-H), 7.73-7.75 (d, 1H, Ar-H), 7.83-7.88 (d, 1H, Ar-H) ppm. MS *m/z* 375 (M^+, 30), 298 (100). Anal. Calcd for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19. Found: C, 67.21; H, 4.54; N, 11.18.

2.3.2. Ethyl 1-amino-3-(4-chlorophenyl)-2-cyano-3*H*-benzo[4,5]thiazolo[3,2-*a*]-pyridine-4-carboxylate (5b)

Yellow; Mp 198-200°C; FTIR (KBr, cm^{-1}): 3420, 3325 (NH_2), 2221 (CN), 1667 (CO-ester). ^1H NMR (DMSO-d_6, 300 MHz): 1.19 (t, 3H, $\underline{CH_3}CH_2$), 4.12-4.15 (q, 2H, $CH_3\underline{CH_2}$), 4.63 (s, 1H, 3H-pyridine), 6.53 (brs, 2H, NH_2; cancelled by D_2O), 7.16-7.37 (m, 6H, Ar-H), 7.73-7.76 (d, 1H, Ar-H), 7.85-7.88 (d, 1H, Ar-H) ppm. MS *m/z* 409 (M^+, 37), 298 (100). Anal. Calcd for $C_{21}H_{16}ClN_3O_2S$: C, 61.53; H, 3.93; N, 10.25. Found: C, 61.51; H, 3.92; N, 10.27.

2.3.3. Ethyl 1-amino-2-cyano-3-(4-methoxyphenyl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]-pyridine-4-carboxylate (5c)

Yellow; Mp 175-177°C; FTIR (KBr, cm^{-1}): 3432, 3342 (NH_2), 2188 (CN), 1666 (CO-ester). ^1H NMR (DMSO-d_6, 300 MHz): 1.20 (t, 3H, $\underline{CH_3}CH_2$), 3.67 (s, 3H, OCH_3), 4.13 (q, 2H, $CH_3\underline{CH_2}$), 4.54 (s, 1H, 3H-pyridine), 6.48 (brs, 2H, NH_2; cancelled by D_2O), 6.82-6.85 (d, 2H, Ar-H), 7.05-7.08 (d, 2H, Ar-H), 7.23 (t, 1H, Ar-H), 7.34 (t, 1H, Ar-H), 7.71-7.74 (d, 1H, Ar-H), 7.85-7.88 (d, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 15.45, 36.43, 56.18, 61.42, 68.21, 99.71, 115.31, 117.76, 121.53, 123.49, 123.92, 125.49, 127.43, 128.57, 137.50, 138.03, 151.46, 151.86, 159.43, 164.23. MS *m/z* 405 (M^+, 32), 298 (100). Anal. Calcd for $C_{22}H_{19}N_3O_3S$: C, 65.17; H, 4.72; N, 10.36. Found: C, 65.18; H, 4.74; N, 10.38 ppm.

2.3.4. Ethyl 1-amino-2-cyano-3-(4-hydroxyphenyl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]-pyridine-4-carboxylate (5d)

Greenish yellow; Mp 224-226°C; FTIR (KBr, cm^{-1}): 3455 (OH), 3415, 3365 (NH_2), 2252 (CN), 1669 (CO-ester). ^1H NMR (DMSO-d_6, 300 MHz): 1.25 (t, 3H, $\underline{CH_3}CH_2$), 4.19 (q, 2H, $CH_3\underline{CH_2}$), 4.51 (s, 1H, 3H-pyridine), 6.55 (brs, 2H, NH_2; cancelled by D_2O), 6.57-6.59 (d, 1H, Ar-H), 6.76-6.80 (d, 1H, Ar-H), 6.95 (s, 1H, Ar-H), 7.34 (t, 1H, Ar-H), 7.39 (t, 1H, Ar-H), 7.82-7.85 (d, 1H, Ar-H), 7.96-7.99 (d, 1H, Ar-H), 8.90 (s, 1H, OH; cancelled by D_2O) ppm. MS *m/z* 391 (M^+, 39), 298 (100). Anal. Calcd for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.73. Found: C, 64.45; H, 4.40; N, 10.74.

2.3.5. Ethyl 1-amino-2-cyano-3-(3-hydroxy-4-methoxyphenyl)-3*H*-benzo[4,5]thia-zolo[3,2-*a*]pyridine-4-carboxylate (5e)

Yellow; Mp 218-220°C; FTIR (KBr, cm^{-1}): 3461 (OH), 3402, 3366 (NH_2), 2220 (CN), 1666 (CO-ester). ^1H NMR (DMSO-d_6, 300 MHz): 1.24 (t, 3H, $\underline{CH_3}CH_2$), 3.66 (s, 3H, OCH_3), 4.16 (q, 2H, $CH_3\underline{CH_2}$), 4.52 (s, 1H, 3H-pyridine), 6.45 (brs, 2H, NH_2; cancelled by D_2O), 6.52-6.54 (d, 1H, Ar-H), 6.66-6.69 (d, 1H, Ar-H), 6.75 (s, 1H, Ar-H), 7.23 (t, 1H, Ar-H), 7.35 (t, 1H, Ar-H), 7.71-7.74 (d, 1H, Ar-H), 7.86-7.89 (d, 1H, Ar-H), 8.86 (s, 1H, OH; cancelled by D_2O) ppm. MS *m/z* 421 (M^+, 41), 298 (100). Anal. Calcd for $C_{22}H_{19}N_3O_4S$: C, 62.69; H, 4.54; N, 9.97. Found: C, 62.71; H, 4.53; N, 9.99.

2.4. Synthesis of 6

A Solution of **3** (2.21 g, 10 mmol) in ethanol was added to mixture of ethanolic solution of ethoxymethylene malononitrile **(4f)** (1.22 g, 10 mmol) and TEA. The mixture was stirred at room temperature for 4 hr. until complete precipitation. The solid formed was filtered off, washed by ethanol and recrystalized from ethanol to give compound **6**.

2.4.1. Ethyl 2-cyano-1-imino-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate (6)

Pal yellow; Mp 188-190°C; FTIR (KBr, cm^{-1}): 3464 (NH), 2218 (CN), 1683 (CO-ester). ^1H NMR (DMSO-d_6, 300 MHz): 1.33 (t, 3H, $\underline{CH_3}CH_2$), 4.29 (q, 2H, $CH_3\underline{CH_2}$), 7.56-7.61 (m, 2H, Ar-H), 8.07 (s, 1H, CH=pyridine), 8.11-8.13 (d, 1H, Ar-H), 8.32 (brs, 1H, NH; cancelled by D_2O), 9.60-9.62 (d, 1H, Ar-H) ppm. MS *m/z* 297 (M^+, 100). Anal. Calcd for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13. Found: C, 60.57; H, 3.72; N, 14.15.

2.5. Synthesis of Compound 8

Ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** (2.21 g, 10 mmol) and 3-(substituted phenyl)-2-cyanoacrylate **(7a-c)** (10 mmol) were mixed together in methanolic/TEA solution. The reaction mixture was stirred at room temperature for 4 hr. until complete precipitation. The soled formed was collected and washed with methanol and recrystallized from ethanol/benzene mixture (1:1) to give compound **8**.

2.5.1. Ethyl 2-(amino(methoxy)methyl)-1-oxo-3-phenyl-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate (8a)

Pal yellow; Mp 173-175°C; FTIR (KBr, cm^{-1}): 3465, 3373 (NH_2), 1671 (CO-ester), 1654 (CO-amide). ^1H NMR (DMSO-d_6, 300 MHz): 1.21 (t, 3H, $\underline{CH_3}CH_2$), 3.66 (s, 3H, OCH_3), 4.17-4.22 (q, 2H, $CH_3\underline{CH_2}$), 5.10 (s, 1H, CH), 7.14-7.28 (m, 6H, Ar-H), 7.37 (t, 1H, Ar-H), 7.55 (brs, 2H, NH_2; cancelled by D_2O), 7.73-7.76 (d, 1H, Ar-H), 7.85-7.87 (d, 1H, Ar-H) ppm. MS *m/z* 408 (M^+, 49), 331 (100). Anal. Calcd for $C_{22}H_{20}N_2O_4S$: C, 64.69; H, 4.94; N, 6.86. Found: C, 64.70; H, 4.96; N, 6.88.

2.5.2. Ethyl 2-(amino(methoxy)methyl)-3-(4-chlorophenyl)-1-oxo-1*H*-benzo[4,5]thia-zolo[3,2-*a*]pyridine-4-carboxylate (8b)

Yellowish; Mp 187-189°C; FTIR (KBr, cm^{-1}): 3473, 3399 (NH_2), 1671 (CO-ester), 1657 (CO-amide). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.23 (t, 3H, $\underline{CH_3}CH_2$), 3.65 (s, 3H, OCH_3), 4.17-4.22 (q, 2H, $CH_3\underline{CH_2}$), 5.08 (s, 1H, CH), 7.14-7.17 (d, 2H, Ar-H), 7.26-7.29 (d, 2H, Ar-H), 7.57 (brs, 2H, NH_2; cancelled by D_2O), 7.35-7.43 (m, 2H, Ar-H), 7.74-7.76 (d, 1H, Ar-H), 7.84-7.87 (d, 1H, Ar-H) ppm. MS *m/z* 442 (M^+, 44), 331 (100). Anal. Calcd for $C_{22}H_{19}ClN_2O_4S$: C, 59.66; H, 4.32; N, 6.32. Found: C, 59.68; H, 4.33; N, 6.30.

2.5.3. Diethyl 1-amino-3-(4-methoxyphenyl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-2,4-dicarboxylate (8c)

Yellow; Mp 204-206 °C; FTIR (KBr, cm^{-1}): 3409, 3306, 3205 (NH_2), 1669, 1675 (2CO). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.20 (t, 3H, $\underline{CH_3}CH_2$), 1.24 (t, 3H, $\underline{CH_3}CH_2$), 3.65 (s, 3H, OCH_3), 4.11 (q, 2H, $CH_3\underline{CH_2}$), 4.18 (q, 2H, $CH_3\underline{CH_2}$), 5.03 (s, 1H, 3H-pyridine), 6.75-6.78 (d, 2H, Ar-H), 7.04-7.07 (d, 2H, Ar-H), 7.25 (t, 1H, Ar-H), 7.36 (t, 1H, Ar-H), 7.49 (brs, 2H, NH_2; cancelled by D_2O), 7.73-7.76 (d, 1H, Ar-H), 7.84-7.87 (d, 1H, Ar-H) ppm. MS *m/z* 452 (M^+, 36), 345 (100). Anal. Calcd for $C_{24}H_{24}N_2O_5S$: C, 63.70; H, 5.35; N, 6.19. Found: C, 63.68; H, 5.36; N, 6.21.

2.6. Synthesis of Compound 9

A mixture of β-enaminonitrile **5c** (4.05 g, 10 mmol), triethylorthoformate (10 mmol) and Ac_2O (30 ml) was refluxed for 3 h. The solvent was removed under reduced pressure and the resulting solid was washed with ethanol, dried and crystallized from benzene to give **9**.

2.6.1. Ethyl 2-cyano-1-((ethoxymethylene)amino)-3-(4-methoxyphenyl)-3*H*-benzo-[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate (9)

Yellow; Mp 135-137°C; FTIR (KBr, cm^{-1}): 2202 (CN), 1672 (CO-ester). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.16 (t, 3H, $\underline{CH_3}CH_2$), 1.35 (t, 3H, $O\underline{CH_3}CH_2$), 3.72 (s, 3H, OCH_3), 4.06-4.13 (m, 2H, $CH_3\underline{CH_2}$), 4.43-4.46 (m , 2H, $OCH_3\underline{CH_2}$), 4.73 (s, 1H, 3H-pyridine), 6.88-6.91 (d, 2H, Ar-H), 7.21-7.24 (m, 3H, Ar-H), 7.28-7.34 (t, 1H, Ar-H), 7.68-7.70 (d, 1H, Ar-H), 7.77-7.80 (d, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 14.19, 14.21, 36.97, 55.08, 60.26, 64.59, 80.04, 96.15, 114.11, 117.01, 119.20, 122.47. 124.39, 126.18, 126.71, 128.22, 136.34, 136.64, 150.14, 151.65, 158.56, 165.76 ppm. MS *m/z* 461 (M^+, 33), 354 (100). Anal.Calcd for $C_{25}H_{23}N_3O_4S$: C, 65.06; H, 5.02; N, 9.10. Found: C, 65.10; H, 5.06; N, 9.08.

2.7. Reaction with Anime Derivatives

A mixture of **9** (4.61 g, 10 mmol), hydrazine hydrate, 2-aminoethanol, ethane-1,2-diamine, or propane-1,3-diamine (10 mmol) in EtOH was stirred at room temperature for 4 hr. The solid formed was collected and washed by ethanol. All compounds were recrystallized from dioxan to give compound **10**.

2.7.1. Ethyl 3-amino-4-imino-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-benzo[4',5']thia-zolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxylate (10a)

Pal yellow; Mp 203-205°C; FTIR (KBr, cm^{-1}): 3322, 3315, 3300, 3266 (NH_2 and NH), 1672 (CO). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.23 (t, 3H, $\underline{CH_3}CH_2$), 3.66 (s, 3H, OCH_3), 4.09-4.16 (q, 2H, $CH_3\underline{CH_2}$), 5.18 (brs, 2H, NH_2; cancelled by D_2O), 5.76 (s, 1H, 5H-pyridine), 6.77-6.80 (d, 2H, Ar-H), 6.98 (brs, 1H, NH; cancelled by D_2O), 7.21-7.36 (m, 4H, Ar-H), 7.67-7.70 (d, 1H, Ar-H), 8.19 (s, 1H, CH-pyrimidine), 8.53-8.56 (d, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 14.31, 36.72, 54.95, 59.94, 96.04, 113.52, 118.22, 122.03, 123.74, 125.88, 126.82, 128.61, 136.70, 137.19, 145.62, 150.63, 158.03, 166.03 ppm. MS *m/z* 447 447 (M^+, 41), 340 (100). Anal. Calcd for $C_{23}H_{21}N_5O_3S$: C, 61.73; H, 4.73; N, 15.65. Found: C, 61.74; H, 4.75; N, 15.67.

2.7.2. Ethyl 3-(2-hydroxyethyl)-4-imino-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-benzo-[4',5']thiazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxylate (10b)

Yellowish; Mp 192-194°C; FTIR (KBr, cm^{-1}): 3443 (OH), 3335, 3318, 3330, 3266 (NH_2 and NH), 1666 (CO). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.25 (t, 3H, $\underline{CH_3}CH_2$), 3.53 (t, 2H, $\underline{CH_2}$-N), 3.67 (s, 3H, OCH_3), 3.98 (t, 2H, $\underline{CH_2}OH$), 4.09-4.17 (q, 2H, $CH_3\underline{CH_2}$), 5.04 (s, 1H, 5H-pyridine), 6.79-6.82 (d, 2H, Ar-H), 7.19-7.37 (m, 4H, Ar-H), 7.67-7.70 (d, 1H, Ar-H), 8.09 (brs, 1H, NH; cancelled by D_2O), 8.23 (s, 1H, CH-pyrimidine), 8.55-8.58 (d, 1H, Ar-H) ppm. MS *m/z* 476 (M^+, 46), 369 (100). Anal. Calcd for $C_{25}H_{24}N_4O_4S$: C, 63.01; H, 5.08; N, 11.76. Found: C, 63.04; H, 5.10; N, 11.74.

2.7.3. Ethyl 3-(2-aminoethyl)-4-imino-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-benzo-[4',5']thiazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxylate (10c)

Pal yellow; Mp 188-190°C; FTIR (KBr, cm^{-1}): 3426 (br, NH_2, NH), 1671 (CO). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.25 (t, 3H, $\underline{CH_3}CH_2$), 2.08-2.09 (m, 4H, N-$\underline{CH_2}\underline{CH_2}$-N), 3.67 (s, 3H, OCH_3), 4.10-4.18 (m, 4H, $CH_3\underline{CH_2}$ + NH_2; cancelled by D_2O), 5.10 (s, 1H, 5H-pyridine), 6.79-6.82 (d, 2H, Ar-H), 7.19 (t, 1H, Ar-H), 7.24-7.29 (m, 3H, Ar-H), 7.64-7.66 (d, 1H, Ar-H), 7.85 (brs, 1H, NH; cancelled by D_2O),8.11 (s, 1H, CH-pyrimidine), 8.41-8.44 (d, 1H, Ar-H) ppm. MS *m/z* 475 (M^+, 33), 368 (100). Anal. Calcd for $C_{25}H_{25}N_5O_3S$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.12; H, 5.32; N, 14.76.

2.7.4. Ethyl 3-(3-aminopropyl)-4-imino-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-benzo-[4',5']thiazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxylate (10d)

Pal yellow; Mp 210-212°C; FTIR (KBr, cm^{-1}): 3433 (br, NH_2, NH), 1661 (CO). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.28 (t, 3H, $\underline{CH_3}CH_2$), 1.89 (m, 2H, N-$CH_2\underline{CH_2}CH_2$-NH_2), 3.18 (t, 2H, N-$CH_2CH_2\underline{CH_2}$-NH_2), 3.61 (t, 2H, N-$\underline{CH_2}CH_2CH_2$-NH_2), 3.69 (s, 3H, OCH_3), 4.05-4.18 (m, 4H, $CH_3\underline{CH_2}$ + NH_2; cancelled by D_2O), 5.09 (s, 1H, 5H-pyridine), 6.99-6.81 (d, 2H, Ar-H), 7.19-7.36 (m, 4H, Ar-H), 7.56-7.60 (d, 1H, Ar-H). 8.10 (brs, 1H, NH; cancelled by D_2O), 8.21 (s, 1H, CH-pyrimidine), 8.62-8.66 (d, 1H, Ar-H) ppm. MS *m/z* 489 (M^+, 41), 382 (100). Anal. Calcd for $C_{26}H_{27}N_5O_3S$: C, 63.78; H, 5.56; N, 14.30. Found: C, 63.80; H, 5.57; N, 14.34.

2.8. Synthesis of Compound 11

Mixture of **10a** (2.24g, 5 mmol) and benzaldehyde (5 mmol) were refluxed in ethanol in presence of piperidine (0.5 mL) for 4 hrs. The solvent was removed under reduced pressure and the solid formed was collected by filtration, washed by ethanol and crystallized from ethanol/benzene mixture (1:1) to give compound **11**.

2.8.1. (*E*)-ethyl3-(benzylideneamino)-4-imino-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-*d*]pyrimidine-6-carboxylate (11)

Yellow; Mp 213-215°C; FTIR (KBr, cm^{-1}): 3311 (NH), 1666 (CO-ester). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.23 (t, 3H, $\underline{CH_3}CH_2$), 3.63 (s, 3H, OCH_3), 4.20 (q, 2H, $CH_3\underline{CH_2}$), 5.75 (s, 1H, 5H-pyridine), 6.79-6.83 (d, 2H, Ar-H), 7.31-7.57 (m, 5H, Ar-H + NH), 7.77-7.80 (d, 1H, Ar-H), 8.25 (s, 1H, CH=N), 8.53-8.71 (d, 1H, Ar-H), 9.77 (s, 1H, CH-pyrimidine) ppm. MS *m/z* 535 (M^+, 42), 428 (100). Anal. Calcd for $C_{30}H_{25}N_5O_3S$: C, 67.27; H, 4.70; N, 13.08. Found: C, 67.25; H, 4.72; N, 13.11.

2.9. Synthesis of Compounds 12a,b

A solution of **10a** (2.24 g, 5 mmol) and ethyl cyanoacetate (0.57 g, 5 mmol) or triethyorthoformate (0.75 g, 5 mmol) in dry ethanol (30 mL) was refluxed for 3 h to give **12a,b**.The solids formed were collected by filtration, washed with ethanol and recrystallized from dioxan.

2.9.1. Ethyl 4-(4-methoxyphenyl)-4*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[3,2-*e*]-[1,2,4]triazolo[1,5-*c*]pyrimidine-5-carboxylate (12a)

Yellow; Mp 275-277°C; FTIR (KBr, cm^{-1}): 1678 (CO-ester). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.18 (t, 3H, $\underline{CH_3}CH_2$), 3.63 (s, 3H, OCH_3), 4.11 (q, 2H, $CH_3\underline{CH_2}$), 5.66 (s, 1H, 4H-pyridine), 6.74-6.76 (d, 2H, Ar-H), 7.23-7.44 (m 4H, Ar-H), 7.73-7.77 (d, 1H, Ar-H), 8.62-8.64 (d, 1H, Ar-H), 9.75 (s, 1H, triazole-H), 9.77 (s, 1H, pyrimidine-H) ppm. MS *m/z* 457 (M^+, 28), 350 (100). Anal. Calcd for $C_{24}H_{19}N_5O_3S$: C, 63.01; H, 4.19; N, 15.31. Found: C, 62.98; H, 4.21; N, 15.29.

2.9.2. Ethyl 2-(cyanomethyl)-4-(4-methoxyphenyl)-4*H*-benzo[4',5']thiazolo[3',2':1,6]-pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5-carboxylate (12b)

Yellow; Mp 253-255°C; FTIR (KBr, cm^{-1}): 2221 (CN), 1672 (CO-ester). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.22 (t, 3H, $\underline{CH_3}CH_2$), 3.63 (s, 3H, OCH_3), 4.12-4.17 (q, 2H, $CH_3\underline{CH_2}$), 4.51 (s, 2H, CH_2CN), 5.63 (s, 1H, 4H-pyridine), 6.76-6.81 (d, 2H, Ar-H), 7.21-7.43 (m, 4H, Ar-H), 7.75-7.79 (d, 1H, Ar-H), 8.64-8.68 (d, 1H, Ar-H), 9.78 (s, 1H, pyrimidine-H) ppm. MS *m/z* 496 (M^+, 12), 389 (100). Anal. Calcd for $C_{26}H_{20}N_6O_3S$: C, 62.89; H, 4.06; N, 16.93. Found: C, 62.91; H, 4.09; N, 16.95.

2.10. Synthesis of Compounds 12c

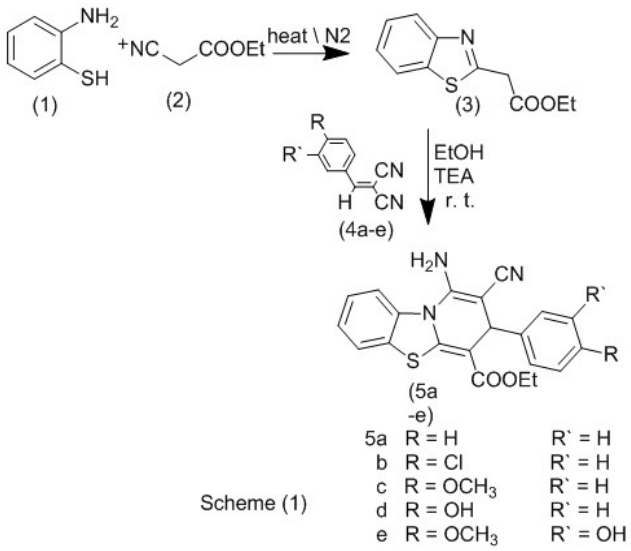
A mixture of **10a** (2.24 g, 5 mmol) and acetyl chloride (0.5 g, 5 mmol) were refluxed in dry benzene for 4 hrs. The solvent was removed under reduced pressure to give a yellowish solid which was collected by filtration, washed with ethanol and crystallized from dioxan to give compound **12c**.

2.10.1. Ethyl 4-(4-methoxyphenyl)-2-methyl-4*H*-benzo[4',5']thiazolo[3',2':1,6]-pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5-carboxylate (12c)

Yellowish; Mp 281-283°C; FTIR (KBr, cm^{-1}): 1679 (CO-ester). ^{1}H NMR (DMSO-d_6, 300 MHz): 1.22 (t, 3H, $\underline{CH_3}CH_2$), 2.40 (s, 3H, CH_3-triazole), 3.63 (s, 3H, OCH_3), 4.13 (q, 2H, $CH_3\underline{CH_2}$), 5.61 (s, 1H, 4H-pyridine), 6.76-6.81 (d, 2H, Ar-H), 7.21-7.41 (m, 4H, Ar-H), 7.72-7.75 (d, 1H, Ar-H), 8.63-8.67 (d, 1H, Ar-H), 9.62 (s, 1H, pyrimidine-H); ^{13}C NMR (75 MHz, DMSO-d_6): 14.28, 14.35, 37.16, 54.95, 60.18, 95.08, 97.02, 105.78, 113.91, 117.76, 122.23, 124.26, 126.12, 126.76, 128.30, 136.03, 136.77, 143.35, 152.73, 158.22, 166.27 ppm. MS *m/z* 471 (M^+, 29), 364 (100). Anal. Calcd for $C_{25}H_{21}N_5O_3S$: C, 63.68; H, 4.49; N, 14.85. Found: C, 63.70; H, 4.50; N, 14.87.

3. Results and Discussion

Thus reaction of **3** with arylidenemalononitrile **(4a-e)** in EtOH/TEA solution was performed at room temperature to give ethyl 1-amino-2-cyano-3-(substituedphenyl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate **(5a-e)** Scheme (1).



Scheme (1)

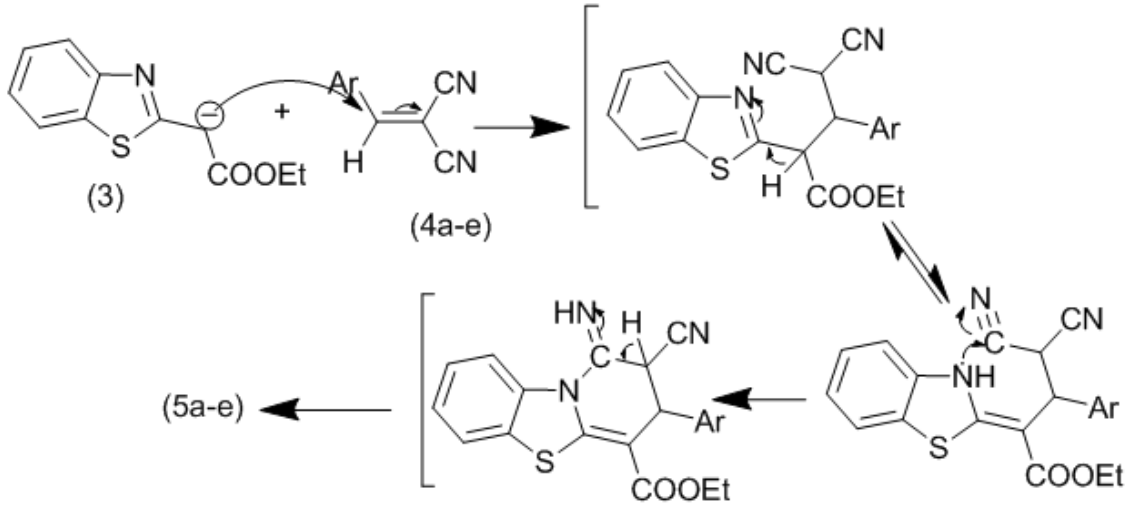
Scheme 1.

The chemical structure of compound **5** was established on the basis of its spectral data. The IR of **5a** showed (NH_2) at 3430, 3337 and (CN) at 2186 while the (CO-ester) resonated at 1668. ^{1}HNMR showed (CH_3) at 1.20 and (CH_2) at 4.11-4.17 while the 3H-pyridine resonated at 4.61. The (NH_2) appeared at 6.49 as a broad singlet. The mass spectroscopy of **5a** showed a molecular ion peak at 375.

Also, the ^{1}H NMR for compounds **5b-e** showed peaks at 4.63, 4.54, 4.58 and 4.52, respectively; corresponding to 3H-pyridine while the (NH_2) group was resonated at 6.53, 6.48, 6.44 and 6.45, respectively.

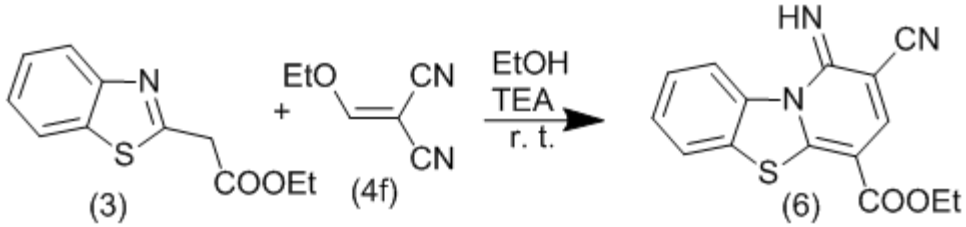
The ^{13}C NMR of compound **5c** showed signals at 15.45, 68.21 corresponding to the (CH_3-CH_2-ester) while the (OCH_3) appeared at 56.18. The 3C-pyridine appeared at 99.71 while the (CN) showed at 117.76. The (CO-ester) resonated at 159.43.

Formation of compound **5** is assumed to proceed via Michael addition of ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** to ylidenic bond in **4** forming an acyclic intermediate, which cyclized by nucleophilic attack of the NH on the cyanocarbon followed by tautomerization to the final product **5** (Scheme 2).



Scheme 2.

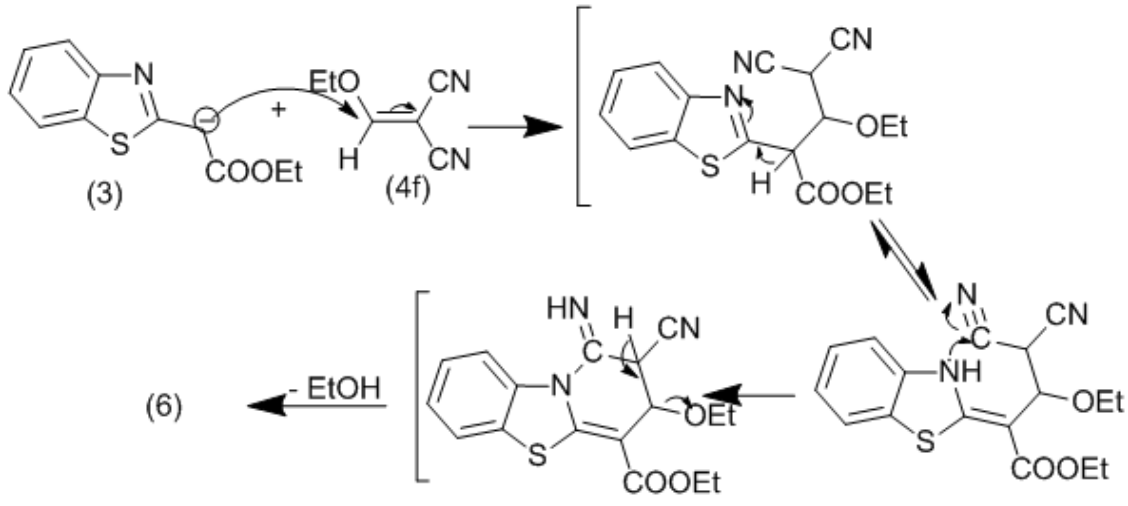
When **3** was reacted with 2-(ethoxymethylene)malononitrile **(4f)** under the same reaction conditions, ethyl 2-cyano-1-imino-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate **(6)** was obtained (Scheme 3).



Scheme 3.

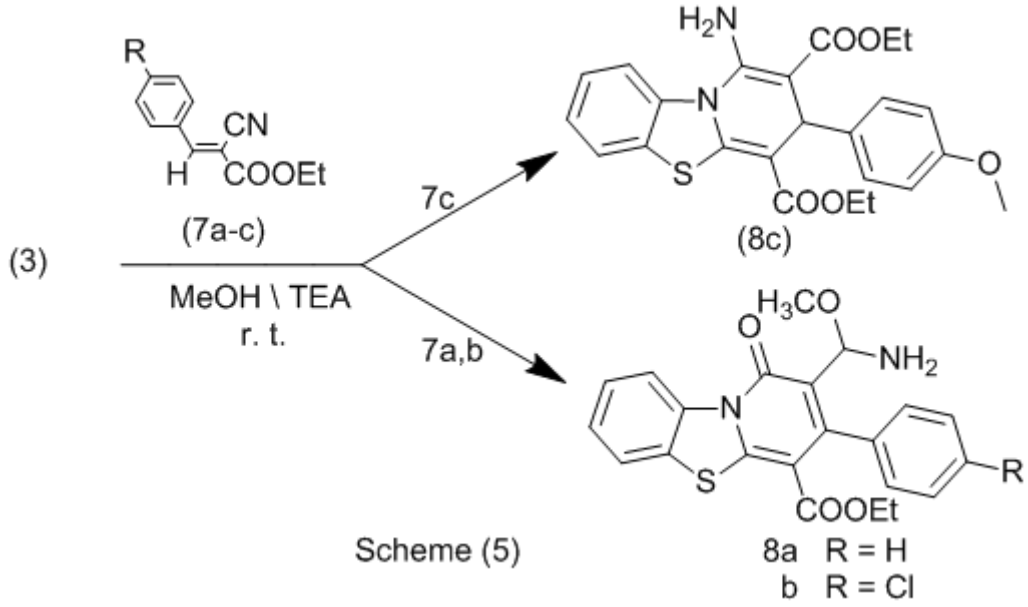
The chemical structure of compound **6** was confirmed on the basis of its spectral data. IR of compound **6** showed the absence of (NH_2) and appearance of absorption peak at 3464 for (NH), while (CN) was observed at 2218 and (CO-ester) resonated at 1683. The ^{1}H NMR showed peaks at 1.33 and 4.29 corresponding to the (CH_3CH_2-ester) while a peak at 8.07 was appeared equivalent to (pyridine-CH=). A broad singlet was also observed at 8.38 corresponding to the (NH) group. The mass spectrum of compound **6** showed a molecular ion at 297.

Formation of compound **6** is also assumed to proceed via Michael addition of ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** to ylidenic bond in **4f** followed by formation of an acyclic intermediate, which cyclized by nucleophilic attack of the NH on the cyanocarbon and then followed by elimination of one ethanol molecule to give the final product **6** (Scheme 4).



Scheme 4.

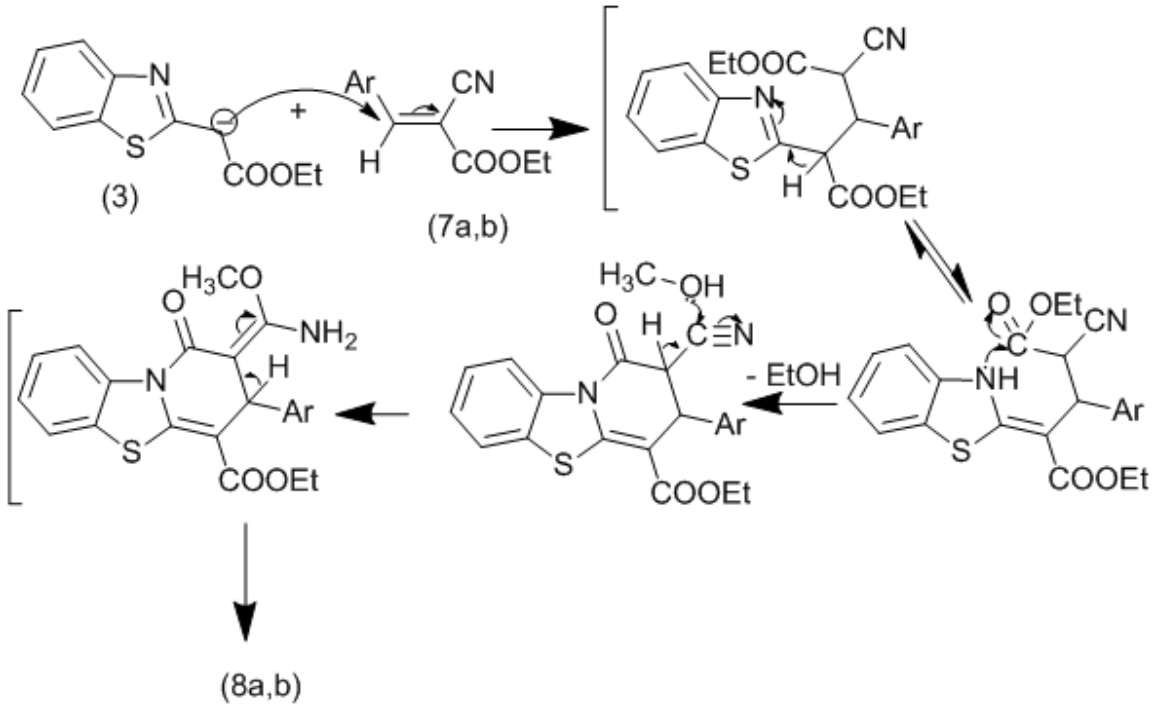
Interaction of **3** with ethyl 3-(substituted phenyl)-2-cyanoacrylate **(7a-c)** in MeOH/TEA at room temperature gave, in case of **7a,b**, ethyl 2-(amino(methoxy)methyl)-3-(substituted phenyl)-1-oxo-1*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate **(8a,b)** while diethyl 1-amino-3-(4-methoxyphenyl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-2,4-dicarboxylate **(8c)** was obtained, in case of **7c** (Scheme 5).



Scheme 5.

The chemical structure of these compounds **(8a-c)** has been elucidated depending on their spectroscopic analysis. IR for compounds **8a,b** showed absorption peaks for (NH_2) at 3465, 3373 and 3473, 3399 cm^{-1}; respectively. Other peaks have been detected at 1671 corresponding to the (CO-ester) in addition to absorption peak at 1654 and 1657 for (CO-amide). ^{1}H NMR for both **8a,b** showed a new signal at 3.66 and 3.65 equivalent to (OCH_3) while singlet at 5.10 and 5.08 has been observed corresponding to (-CH-) for the methyl-side chain. The signal corresponding to 3H-pyridine was not detected. The mass spectrum of **8a** gave a molecular ion peak at 408. Compound **8c** showed signals at 1.20, 1.24 and 4.11, 4.18 corresponding to the ($2CH_3CH_2$-ester). The mass spectroscopy showed a molecular ion peak at 452.

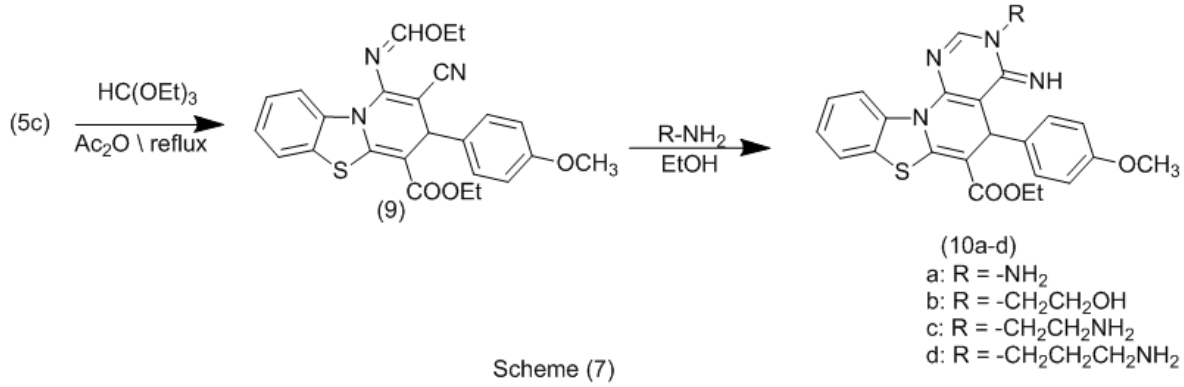
The formation of compounds **8a,b** could be attributed to the formation of a Michael adduct followed by nucleophilic attack of the NH on the carbonyl-carbon with elimination of ethanol followed by solvolysis of the nitrile group and tautomirization to give the final product **8a,b** (Scheme 6).



Scheme 6.

Unfortunately, attempts to react **5** with different reagents such as acetic anhydride, acetyl chloride, benzoyl chloride, chroroacetyl chloride, aromatic aldehydes and alkyl cyanides under different reaction conditions were unsuccessful.

Treatment of **5c** with triethylorthoformate in acetic anhydride at refluxing temperature gave the correspondingethyl 2-cyano-1-((ethoxymethylene)amino)-3-(4-methoxyphenyl)-3*H*-benzo[4,5]thiazolo[3,2-*a*]pyridine-4-carboxylate **(9)** which was treated with different amines to afford the ethyl 3-substituted-4-imino-5-(4-methoxyphenyl)-4,5-dihydro-3*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-d]py-rimidine-6-carboxylate **(10a-d)** (Scheme 7).



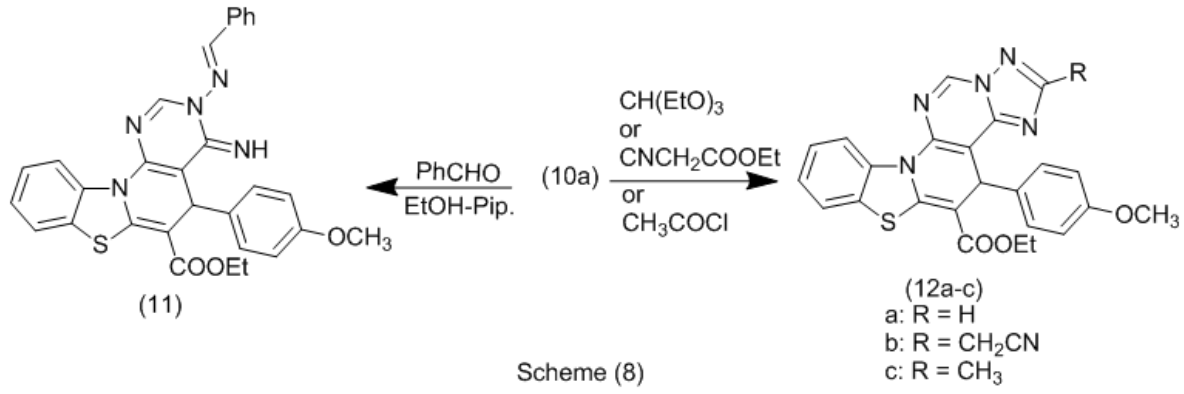
Scheme (7)

Scheme 7.

The structures of compound **9** and **10** were established on the basis of IR, ^{1}H NMR, ^{13}C NMR and MS data. The IR spectra of compounds **9** showed the presence of CN stretches at 2202 cm^{-1} and a peak at 1672 corresponding to the (CO-ester). The ^{13}C NMR showed signals at 14.19 (CH_3-ester), 14.21 (CH_3-ethoxy), 60.26 (CH_2-ester), 64.59 (CH_2-ethoxy) and (CH=pyrimidine) at 150.14. The mass spectroscopy showed a molecular ion peak at 461. ^{1}H NMR for compounds **10a-d** showed signals at 8.09-8.23 corresponding to (CH=pyrimidine), while the (CH=pyrimidine) was resonated in ^{13}C NMR at 145.62 for **10a**.

The imino compound **10a** proved to be a useful intermediate for the synthesis of a variety of 2-substituted-4*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5-carboxylat-ederivatives. Thus, treatment of **10a**with triethylorthoformate, ethyl cyanoacetate and/or acetyl chloride in different solvents afforded ethyl 4-(4-methoxyphenyl)-4*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyri-midine-5-carboxylate **(12a)**, ethyl 2-(cyanomethyl)-4-(4-methoxyphenyl)-4*H*-benzo-[4',5']thiazolo[3',2':1,6]pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5-carboxylate **(12b)** and ethyl 4-(4-methoxyphenyl)-2-methyl-4*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine-5-carboxylate **(12c)**, respectively (Scheme 8). The ^{1}H NMR spectra of **12** showed signals at 9.62-9.78 corresponding to pyrimidine-H while **12a** showed signal at 9.75 corresponding to triazolo-H.

Condensation of **10a** with benzaldehyde under reflux in ethanolic piperidine afforded the open chain productethyl 3-(benzylideneamino)-4-imino-5-(4-methoxy-phenyl)-4,5-dihydro-3*H*-benzo[4',5']thiazolo[3',2':1,6]pyrido[2,3-*d*]pyramidine-6-carbox-ylate **(11)** (Scheme 8). The structure of **11** was established on the basis of its IR spectrum, which showed the presence of NH absorption at 3311 cm^{-1}. The ^{1}H NMR spectra of **11** showed signals at 8.25 (s, 1H, N=CH) and 9.77 (s, 1H, pyrimidine-H).



Scheme (8)

Scheme 8.

4. Conclusion

Ethyl 1-amino-3-(substituted phenyl)-2-cyano-3*h*-benzo[4,5]thiazolo-[3,2-*a*]pyridine-4-carboxylate derivatives **(5a-e)** were prepared by convenient method. Reaction of ethyl 2-(benzo[*d*]thiazol-2-yl)acetate **(3)** with ylidenic compounds resulted in formation of pyridine derivatives **(6, 8a-c)**. When compound **5c** was reacted with triethylorthoformate, the ethoxymethyleneaminopyridine-4-carboxylate derivative **(9)** was obtained. The triazolo[1,5-*c*]pyrimidine-5-carboxylate derivatives **(12a-c)** were obtained when **10a** was reacted with electrophilic reagents.

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