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NITRILES IN ORGANIC SYNTHESIS: SYNTHESIS OF PYRIDO[2,1-*b*]BENZOTHIAZOLE DERIVATIVES AND POLYFUNCTIONALLY-SUBSTITUTED PYRIDINES

M. E. A. Zaki[1], A. A. Fadda[2], K. Samir[2], and F. A. Amer[2]

A variety of pyrido[2,1-b]benzothiazole derivatives could be prepared by reaction of 2-cyanomethylbenzothiazole, formaldehyde, and various active methylene reagents. Also some polyfunctionally-substituted pyridines were prepared by reaction of 2-cyanomethylbenzothiazole, formaldehyde, and an α-functionally substituted acrylonitrile.

Keywords: 2-cyanomethylbenzothiazole, pyridines, pyrido[2,1-*b*]benzothiazoles.

Aldehydes condense with active methylene nitriles to yield the corresponding ylidine derivatives [1]. The reaction of these ylidines with active methylene [2-4] has been extensively utilized for the synthesis of pyridine derivatives. Although α-functionally-substituted acrylonitriles are expected to react similarly with active methylene reagents, thus affording pyridine derivatives, the difficulty of preparing α-functionally-substituted acrylonitriles explains the lack of reports on their utility. In addition, the biological importance of benzothiazole derivatives has resulted in much interest in their synthesis and chemistry [5-11].

As part of our program directed to the development of new simple and efficient procedures for the synthesis of fused heterocyclic nitrogen compounds utilizing readily obtainable nitrile intermediates, we have previously reported several new approaches to the synthesis of condensed heterocycles using 2-cyanomethylbenzothiazolyl derivatives [12] as starting material. In conjunction with our current interest in the synthesis of polysubstituted heterocycles incorporating a benzothiazole moiety, we disclose here a facile synthesis of the highly versatile, hitherto unreported pyridobenzothiazole derivatives. In view of the considerable biological importance of pyridine and benzothiazole, the synthesized compounds containing this structural moiety may possess interesting and useful biological and pharmaceutical properties. It has been found that a mixture of 2-cyanomethylbenzothiazole (**1**) and formaldehyde generates *in situ* 2-(benzothiazol-2-yl)acrylonitrile (**2**) and can thus be considered as a synthetic equivalent of this reagent.

In the present work we report results aimed at exploring the synthetic potentialities of this reagent and also demonstrate results of our trials to produce in the same way other functionally-substituted acrylonitriles. Thus, a mixture of formaldehyde and compound **1** reacted in refluxing ethanol to yield a product which may be formulated as pyridobenzothiazole derivative **3** or 2,4-bis(benzothiazol-2-yl)pentanedinitrile (**4**) (Scheme 1).

[1] Photochemistry Department, National Research Center, Dokki, Cairo, Egypt; e-mail: meazaki@netscape.net. [2] Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1413-1419, September, 2003. Original article submitted April 12, 2002; revision submitted June 26, 2003.

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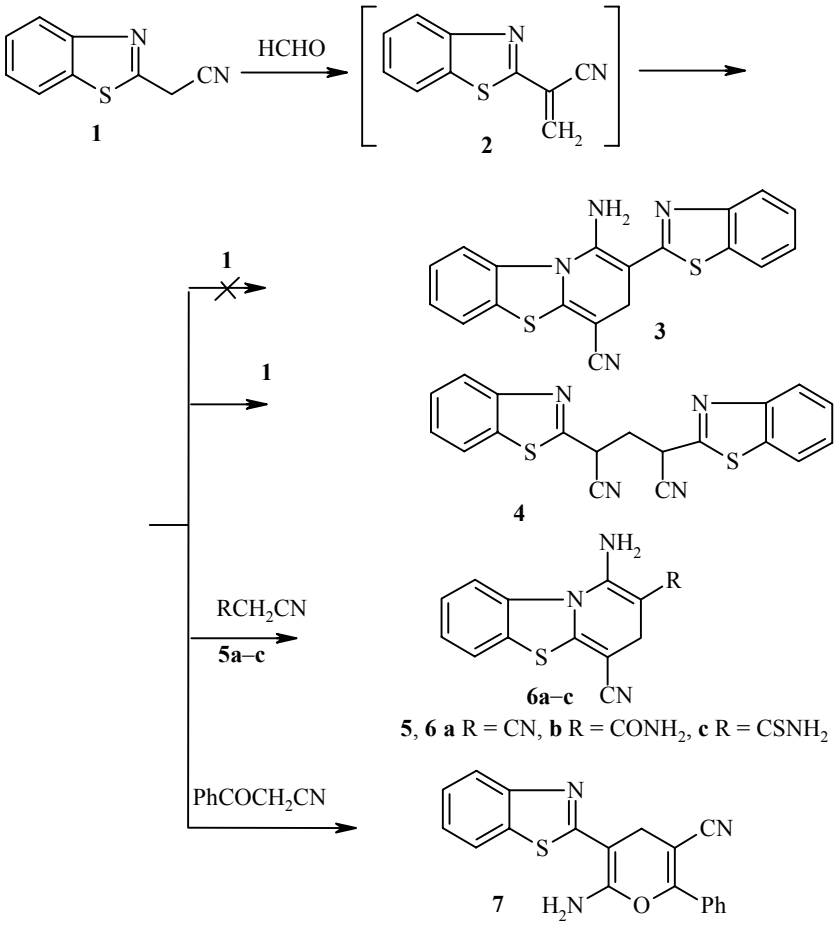
Scheme 1

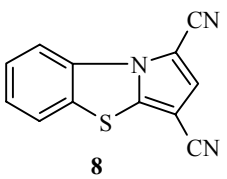


Structure **3** was ruled out on the basis of the ^{1}H NMR spectrum of the reaction product, which revealed the CH_2 protons and CH protons as a multiplet at δ 3.4-3.8 due to vicinal and geminal coupling, and a multiplet at δ 7.1-8.1 ppm due to aromatic protons. In addition, the IR spectrum showed absorption bands near 2220 cm^{-1} indicating the presence of cyano groups and the absence of any bands in the region 3200-3600 cm^{-1} (NH_2 group). The mass spectroscopic measurement showed *m/z:* 360 $[M]^+$.

On the other hand, when a mixture of equimolar amounts of **1**, formaldehyde, and active methylene reagents **5a**-**c** was heated in ethanol and triethylamine, the reaction afforded 1-amino-3H-pyrido[2,1-*b*]-[1,3]benzothiazole-2,4-dicarbonitrile, 1-amino-4-cyano-3H-pyrido[2,1-*b*][1,3]benzothiazole-2-carboxamide, and 1-amino-4-cyano-3H-pyrido[2,1-*b*][1,3]benzothiazole-2-carbothioamide (**6a-c**), respectively (Scheme 1). Their structures were established from analytical and spectral data. For example, compound **6a** had in its IR spectrum absorption bands at 3450-3400 (NH_2) and 2196, 2200 cm^{-1} (CN); the ^{1}H NMR ($CDCl_3$) spectrum showed a singlet at δ 3.2 ppm (CH_2) and a multiplet at δ 7.3-8.4 ppm (H_{Ar} + NH_2 exchangeable with D_2O). Moreover, the mass spectrum revealed a molecular ion peak at *m/z* 252, which was in accordance with its molecular weight.

It was found that a mixture of equimolar amounts of **1,** formaldehyde, and benzoylacetonitrile reacts in refluxing ethanol in the presence of triethylamine to yield 6-amino-5-(1,3-benzothiazol-2-yl)-2-phenyl-4H-pyran-3-carbonitrile (**7**) (Scheme 1). Structure **7** was established by ^{1}H NMR: 4H-pyran protons appeared at δ 4.6 ppm in addition to signals for the amino function and phenyl group, which appeared at δ 6.2 and δ 7.3-8.1 ppm, respectively. Similar results for 4H-pyran protons have been reported previously [13, 14]. The mass spectrum of **7** showed the molecular ion peak *m*/*z* 331 (20%).

Instead of pyrrolobenzothiazole **8** or pyridobenzothiazole **9** derivatives, respectively, compound **1** unexpectedly gave the trisbenzothiazolylacetonitrile derivative **10** in good yield when reacted with a mixture of formaldehyde and chloroacetonitrile in absolute ethanol and in the presence of triethylamine (Scheme 2).



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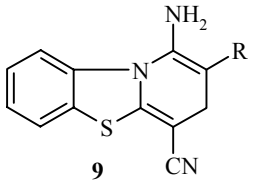

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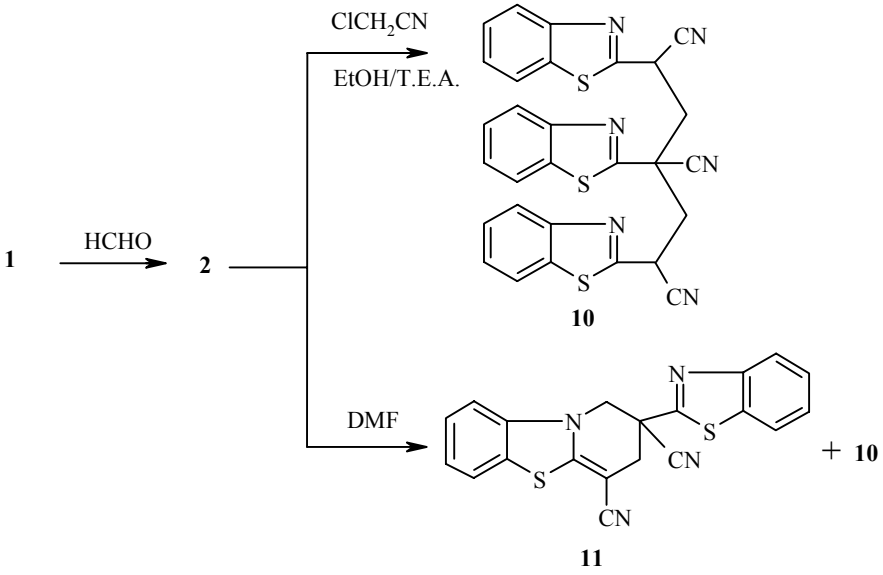
The structure of **10** was established not only on the basis of elemental analysis but also on spectral data. The IR spectrum revealed absorption bands near 2220 and 1600 cm^{-1} characteristic of stretching vibrations of the cyano and C=N function, respectively. The ^1H NMR spectrum showed doublet and triplet signals at δ 2.6 and 3.8 ppm attributable to two methylene protons and two methine protons, respectively, besides the normal aromatic protons at δ 6.8-7.7 ppm. The mass spectroscopic measurement gave also good evidence to the formation of **10**, which showed M^+ = 546. The same reaction took place in the absence of chloroacetonitrile, affording **10**. The formation of **10** was assumed to proceed *via* addition of the α-methylene group of 2-cyanomethylbenzothiazole to the activated double bonds of two molecules of **2** (which is assumed to be formed first). From this proposed reaction mechanism, it was obviously that chloroacetonitrile was not involved in the reaction.

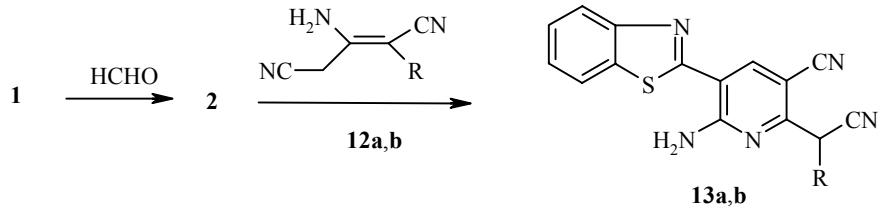
Scheme 2



On the other hand, when the reaction of **1** with formaldehyde was carried out in refluxing DMF for a long time (Scheme 2), it afforded two isolatable products; the first, as the major product, had the molecular formula $C_{20}H_{18}N_6S_3$ (M^+ = 546) corresponding to compound **10** and the second product, as the minor product, had the molecular formula $C_{20}H_{12}N_4S_2$ (M^+ = 372) which can be formulated as 2-(benzothiazol-2-yl)-2,3-dihydro-1H-pyrido[2,1-*b*]benzothiazole-2,4-dicarbonitrile (**11**). The formation of **11** can be explained by the fact that 2-benzothiazol-2-ylacrylonitrile **2** acts as both a highly reactive 1-aza-1,3-diene and as a dienophile to undergo intermolecular cycloaddition, which affords the polycyclic system in a single step. This reaction is considered as a direct approach to nitrogen compounds containing a six-membered ring system *via* hetero Diels–Alder reaction of 1-aza-1,3-butadiene [15].

Polyfunctionally-substituted pyridines are versatile reagents especially as precursors for synthesis of fused heterocyclic pyridine derivatives [16, 17]. It was found (Scheme 3) that 3-amino-2-cyanopent-2-enedinitrile [18] (**12a**) and (2*E*)-3-amino-2-(benzothiazol-2-yl)pent-2-enedinitrile (**12b**) react with formaldehyde to yield [6-amino-5-(benzothiazol-2-yl)-3-cyanopyridin-2-yl]malononitrile (**13a**) and 6-amino-5-(benzothiazol-2-yl)-2-[benzothiazol-2-yl(cyano)methyl]nicotinonitrile (**13b**), respectively.

Scheme 3

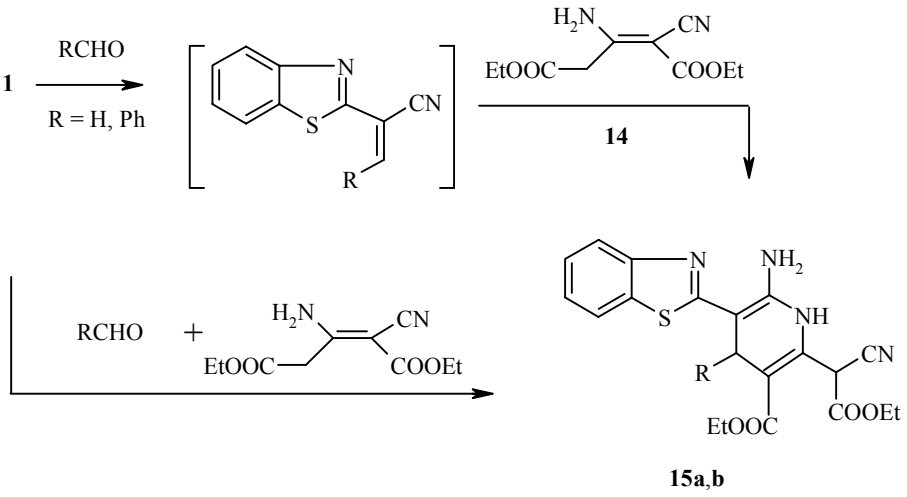


12, 13 a R = CN, **b** R = benzothiazolyl

The product **13a**, as a representative example, showed IR spectrum bands at 2228, 2189 (2 CN), 3367, and 3412 cm^{-1} (NH_2). Its ^1H NMR spectrum contained a singlet signal at δ 5.50 for the methine proton, a broad signal at δ 6.40 for the NH_2 group, a multiplet at δ 7.2-8.1, and a singlet signal at δ 8.8 ppm for the 4-H pyridine proton. Compound **13a** formed a molecular ion peak at *m*/*z* 316 (M^+).

Refluxing an ethanolic solution of equimolar amounts of **1**, diethyl (2*E*)-3-amino-2-cyanopent-2-enedioate (**14**), and formaldehyde or benzaldehyde in the presence of a catalytic amount of triethylamine resulted in 2-amino-3-(benzothiazol-2-yl)-5-carboethoxy-6-carboethoxy(cyano)methyl-1,4-dihydropyridine (**15a**) or 2-amino-3-(benzothiazol-2-yl)-5-carboethoxy-6-carboethoxy(cyano)methyl-4-phenyl-1,4-dihydropyridine (**15b**), respectively. The structures of **15a**,**b** were established on the basis of elemental analysis and spectral data as well as *via* independent synthesis (Scheme 4).

Scheme 4



15 a R = H, **b** R = Ph

EXPERIMENTAL

Melting points were uncorrected. Elemental analysis was carried out in the Microanalytical Unit of the Faculty of Science, Cairo University. IR spectra were recorded on a Pye Unicam SP-1000 cm^{-1} spectrometer using KBr pellet technique. ^1H NMR spectra were determined on Varian Gemini 200 MHz NMR spectrometer using TMS as an internal standard (δ = 0 ppm). Mass spectra were determined on a GC-MS.QP-100 EX. Schimadzu instrument (Japan).

2,4-Bis(benzothiazol-2-yl)pentanedinitrile (4). A mixture of **1** (0.17 g, 1 mmol), formaldehyde (0.1 ml of 30% aqueous solution, 1 mmol) in ethanol (25 ml) in the presence of a catalytic amount of Et_3N was refluxed for 6 h. Yellowish-brown crystals separated during reflux. The crystals were collected by filtration, washed with hot ethanol, and then recrystallized from DMF–ethanol (1:3) to yield 0.32 g of dinitrile **4** (86% yield); mp 158°C. IR spectrum, ν, cm^{-1}: 2220 (CN). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.4-3.8 (m, $2CH_2$ and 2CH protons); 7.1-8.1 (m, 8 aromatic protons). Mass-spectrum: *m/z* 360 $[M]^+$. Found, %: C 62.98; H 3.41; N 15.44. $C_{19}H_{12}N_4S_2$. Calculated, %: C 63.31; H 3.36; N 15.54.

1-Amino-3H-pyrido[2,1-*b*]benzothiazole Derivatives 6a-c (General Procedure). Equimolar amounts of **1** (0.17 g, 1 mmol), formaldehyde (0.1 ml, 30% aqueous solution), and active methylene reagent **5a-c** in ethanol (25 ml) were treated with a catalytic amount of Et_3N. The reaction mixture was refluxed for 6-8 h and the solid product was recrystallized from DMF–ethanol (1:3).

1-Amino-3H-pyrido[2,1-*b*]benzothiazole-2,4-dicarbonitrile (6a). 0.23 g (91% yield); mp 238°C. IR spectrum, ν, cm^{-1}: 2196, 2200 (2CN) and 3450-3400 (NH_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.7 (s, 2H, CH_2); 7.3-8.4 (m, 6H, aromatic protons + NH_2, exchangeable with D_2O). Mass-spectrum: *m/z* 252 $[M^+]$. Found, %: C 61.76; H 3.24; N 22.14. $C_{13}H_8N_4S$. Calculated, %: C 61.89; H 3.20; N 22.21.

1-Amino-4-cyano-3H-pyrido[2,1-*b*]benzothiazole-2-carboxamide (6b). 0.2 g (74% yield); mp 290°C. IR spectrum, ν, cm^{-1}: 2190 (CN) and 3264, 3330, 3420, 3455 ($2NH_2$), 1644 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.8 (s, 2H, CH_2); 4.4, 7.5 (br. s, 4H, $2NH_2$ exchangeable with D_2O); 7.4-8.2 (m, 4H, aromatic protons). Mas-spectrum: *m/z* 270 $[M]^+$. Found, %: C 57.61; H 3.48; N 20.64. $C_{13}H_{10}N_4OS$. Calculated, %: C 57.76; H 3.73; N 20.73.

1-Amino-4-cyano-3H-pyrido[2,1-*b*]benzothiazole-2-carbothioamide (6c). 0.21 g (73% yield); mp 252°C. IR spectrum, ν, cm^{-1}: 2210 (CN) and 3400-3450 ($2NH_2$). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 3.8 (s, 2H, CH_2); 6.7, 7.8 (br. s, 4H, $2NH_2$, exchangeable with D_2O); 7.3-7.9 (m, 4H, aromatic protons). Mass-spectrum: *m/z* 286 $(M]^+$. Found, %: C 54.86; H 3.41; N 19.54. $C_{13}H_{10}N_4S_2$. Calculated, %: C 54.53; H 3.52; N 19.57.

6-Amino-5-(benzothiazol-2-yl)-2-phenyl-4H-pyran-3-carbonitrile (7). Equimolar amounts of 2-cyanomethylbenzothiazole (**1**) (0.17g, 1 mmol), formaldehyde (0.1 ml, 30% aqueous solution), and benzoyl acetonitrile (0.15 g) in ethanol (25 ml) were treated with a few drops of Et_3N. The reaction mixture was refluxed for 6 h and the solid product was recrystallized from DMF–ethanol (1:3) to give **7**: 0.23 g (68% yield); mp 125°C. IR spectrum, ν, cm^{-1}: 2193 (CN) and 3387, 3416 (NH_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 4.9 (s, 2H, 4H pyran protons), 6.8 (br. s, 2H, NH_2); 7.3-8.1 (m, 9H, aromatic protons). Mass-spectrum: *m/z* 331 $[M]^+$. Found, %: C 68.81; H 3.95; N 12.59. $C_{19}H_{13}N_3OS$. Calculated, %: C 68.87; H 3.95; N 12.68.

1,3,5-Tris(benzothiazol-2-yl)-1,3,5-tricyanopentane (10). A mixture of **1** (0.17 g, 1 mmol), formaldehyde (0.1 ml, 30% aqueous solution, 1 mmol), and chloroacetonitrile (0.1 ml, 1 mmol) in ethanol (20 ml) in the presence of a catalytic amount of Et_3N was refluxed for 6 h. The reaction mixture was left to cool at room temperature and the solid product was collected by filtration, dried and recrystallized from ethanol to yield **10**: 0.29 g (53% yield); mp 148°C. IR spectrum, ν, cm^{-1}: 2219 (CN). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.84-3.91 (dd, 4H, $2CH_2$, J = 18.0, J = 9.1); 4.1 (m, 2H, 2 methine protons); 7.5-8.1 (m, 12H, aromatic protons). Mass-spectrum: *m/z* 546 $[M]^+$. Found, %: C 63.78; H 3.16; N 15.54. $C_{29}H_{18}N_6S_3$. Calculated, %: C 63.73; H 3.31; N 15.37.

2-(Benzothiazol-2-yl)-2,3-dihydro-1H-pyrido[2,1-*b*]benzothiazole-2,4-dicarbonitrile (11). A mixture of 1 (0.17 g, 1 mmol), formaldehyde (0.1 ml, 30% aqueous solution, 1 mmol), and chloroacetonitrile (0.1 ml, 1 mmol) in DMF (20 ml) in the presence of a catalytic amount of Et_3N was refluxed for 6 h. The reaction mixture was left to cool at room temperature, the reaction mixture was poured onto ice-cold water, and the solid product was collected by filtration and dried. The solid product was boiled in ethanol, then filtered; the precipitate was **11** and the filtrate was **10** (35%, 0.12 g). Compound **11** was formed in 38 % yield (0.14 g); mp 171°C. IR spectrum, ν, cm^{-1}: 2226 (CN). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.6-3.8 (m, 4H, $2CH_2$); 7.3-8.2 (m, 8H, aromatic protons); Mass-spectrum, *m*/*z*: 372 $[M]^+$. Found, %: C 64.44; H 2.99; N 14.97. $C_{20}H_{12}N_4S_2$. Calculated, %: C 63.71; H 3.24; N 15.04.

6-Amino-5-(benzothiazol-2-yl)-2-[benzothiazol-2-yl(cyano)methyl]nicotinonitrile (13a). Equimolar amounts of **1** (0.17 g, 1 mmol), formaldehyde (0.1 ml, 30% aq. solution, 1 mmol), and 3-amino-2-cyanopent-2-enedinitrile (**12a**) (0.13 g, 1 mmol) in ethanol (25 ml) were treated with a few drops of Et_3N. The reaction mixture was refluxed for 6 h. The reaction mixture was left to cool at room temperature; the solid product was collected by filtration and recrystallized from DMF–ethanol to give 0.26 g (61% yield) of nitrile **13a**; mp 278°C; IR spectrum, ν, cm^{-1}: 2235, 2202 (2CN), 3325, 3407 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.6 (s, 1H, CH); 6.4 (br. s, 2H, NH_2 exchangeable with D_2O); 7.2-8.1 (m, 8H, benzothiazole protons); 8.8 (s, 1H, 4-H pyridine proton). Mass-spectrum: *m/z* 424 $[M]^+$.

[6-Amino-5-(benzothiazol-2-yl)-3-cyanopyridin-2-yl]malononitrile (13b). Equimolar amounts of **1** (0.17 g, 1 mmol), formaldehyde (0.1 ml, 30% aq. solution), and (2*E*)-3-amino-2-(benzothiazol-2-yl)pent-2-enedinitrile (**12b**) (0.24 g) in ethanol (25 ml) were treated with a few drops of Et_3N. The reaction mixture was refluxed for 6 h. The reaction mixture was left to cool at room temperature; the solid product was collected by filtration and recrystallized from ethanol. Nitrile **13b** was obtained (0.22 g, 69.6% yield); mp 240°C. IR spectrum, ν, cm^{-1}: 2228, 2189 (2CN), 3367, 3412 (NH_2). ^{1}HNMR (DMSO-d_6), δ, ppm: 5.5 (s, 1H, CH); 6.4 (br. s, 2H, NH_2, exchangeable with D_2O); 7.2-8.1 (m, 4H, benzothiazole protons); 8.8 (s, 1H, 4-H pyridine proton). Mass-spectrum: *m/z* 316 $[M]^+$. Found, %: C 60.39; H 2.61; N 26.54. $C_{16}H_8N_6S$. Calculated, %: C 60.73; H 2.55; N 26.56.

4-Alkyl-2-amino-3-(benzothiazol-2-yl)-5-carboethoxy-6-carboethoxy(cyano)methyl-1,4-dihydropyridines (15a,b). (General Procedure). Equimolar amounts of **1** (0.17 g, 1 mmol), aldehyde, and compound **14** (0.23 g) in ethanol (25 ml) were treated with a few drops of Et_3N. The reaction mixture was refluxed for 4 h. The reaction mixture was left to cool at room temperature; the solid product was collected by filtration and recrystallized from ethanol.

2-Amino-3-[benzothiazol-2-yl]-5-carboethoxy-6-carboethoxy(cyano)methyl-1,4-dihydropyridine (15a). Yield 0.36 g (87%); mp 237°C. IR spectrum, ν, cm^{-1}: 1688, 1721 (2COOEt), 2212 (CN), 2173 (NH), 3383, 3397 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.1 (t, 3H, Me); 1.3 (t, 3H, Me); 3.2 (s, 2H, CH_2 of pyridine ring); 4.1, 4.2 (q, 4H, $2CH_2$); 4.7 (s, 1H, CH); 7.2-7.8 (m, 4H, aromatic protons); 8.7 (br. s, 2H, NH_2); 11.1 (s, 1H, NH). Mass-spectrum: *m/z* 412 $[M]^+$. Found, %: C 58.08; H 4.87; N 13.59; S 7.69. $C_{20}H_{20}N_4O_4S$. Calculated, %: C 58.24; H 4.89; N 13.58; S 7.77.

2-Amino-3-(benzothiazol-2-yl)-5-carboethoxy-6-carboethoxy(cyano)methyl-4-phenyl-1,4-dihydropyridine (15b). Yield 0.41 g (84%); mp 251°C. IR spectrum, ν, cm^{-1}: 1688, 1721 (2COOEt), 2212 (CN), 2173 (NH), 3283, 3402 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.1 (t, 3H, Me, J = 7.5); 1.3 (t, 3H, Me, J = 7.5); 4.1, 4.3 (q, 4H, $2CH_2$, J = 7.5); 4.6 (s, 1H, CH of pyridine); 5.6 (s, 1H, CH); 7.2-7.8 (m, 9H, aromatic protons); 8.7 (br. s, 2H, NH_2, exchangeable with D_2O); 11.1 (s, 1H, NH, exchangeable with D_2O). Mass-spectrum: *m/z* 488 $[M]^+$. Found, %: C 64.08; H 4.81; N 11.39. $C_{26}H_{24}N_4O_4S$. Calculated, %: C 63.91; H 4.95; N 11.46.

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