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Syntheses with Heterocyclic β-Enaminonitriles: A Facile Preparation of Polyfunctionally Substituted Thiophene, Thieno[3,2-*b*]pyridine and Thieno[3,2-*d*]pyrimidine Derivatives

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Summary. A convenient *Gewald* synthesis of 3,5-diaminothiophene-2-carbonitrile derivatives (**2**) is reported. The synthetic potential of the β-enaminonitrile moiety in **2** has been explored; it proved to be a promising candidate for the synthesis of polyfunctionally substituted thieno[3,2-*b*]pyridines and thieno[3,2-*d*]pyrimidines.

Keywords. Thiophenes; Thieno[3,2-*b*]pyridines; Thieno[3,2-*d*]pyrimidines.

Synthesen mit heterocyclischen β-Enaminonitrilen: Eine einfache Methode zur Herstellung polyfunktionell substituierter Thiophen-, Thieno[3,2-*b*]pyridin- und Thieno[3,2-*d*]pyrimidinderivate

Zusammenfassung. Eine bequeme Methode zur Herstellung von 3,5-Diaminothiophen-2-carbonitril-Derivaten (**2**) nach *Gewald* wird vorgestellt. Das synthetische Potential der β-Enaminonitrilfunktion von **2** wurde untersucht. **2** ist ein geeignetes Ausgangsmaterial für die Synthese polyfunktionell substituierter Thieno[3,2-*b*]pyridine und Thieno[3,2-*d*]pyrimidine.

Introduction

Cyclization of nitriles containing an active methylene group to 2- and 3-aminothiophenes is well documented [1, 2]. In continuation of our interest in thiophene chemistry [3–5], and with a view directed towards preparing biological active heterocycles, we wish to broaden the scope of the *Gewald* reaction utilizing heterocyclic cyanomethylenes as candidates for a facile synthetic route to heterocyclic thiophenes. The work resulted in the formation of some new 3,5-diamino-4-heterocyclic-thiophene-2-carbonitrile derivatives (**2a, b**). The latter could be successfully annelated to polyfunctionally substituted thieno[3,2-*b*]pyridines, thieno[3,2-*d*]pyrimidines, and some other fused thiophenes. The importance of such derivatives is due to their biological and physiological properties. For instance, aminothiophene derivatives are reported to be used as bactericides [6], antiviral drugs [7], inhibitors of thrombocytes [8, 9], and depressants of the central nervous system [10, 11]. Also, thienopyridines [12–14] and thienopyrimidines [15, 16] are reported to exhibit positive biological activity.

Results and Discussion

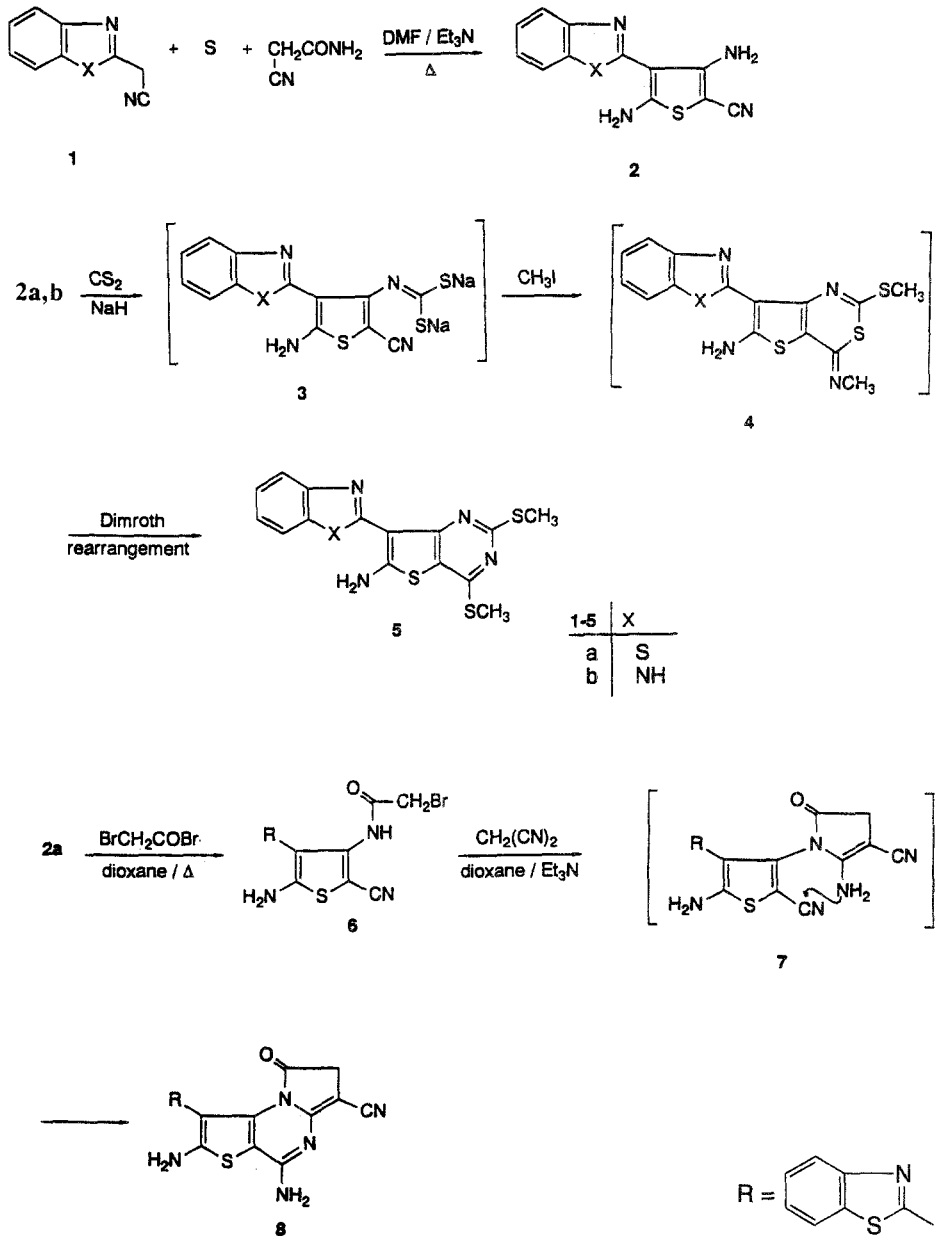
It has been found that heating equimolar amounts of 2-cyanomethylbenzothiazole (**1a**) [17] or 2-cyanomethyl-1*H*-benzimidazole (**1b**) [18], elemental sulfur powder, and cyanoacetamide in dry *DMF* containing a catalytic amount of Et_3N under reflux furnishes exclusively and in reasonable good yields products that could be formulated as 3,5-diamino-4-substituted-thiophene-2-carbonitrile derivatives (**2a, b** Scheme 1). Both elemental and spectroscopic data of **2a, b** are consistent with the assigned structure. Thus, as a representive example, the mass spectrum of **2a** revealed a molecular ion peak at $m/z = 272$ with 28% relative abundance corresponding to the molecular formula $C_{12}H_8N_4S_2$. Its IR spectrum showed absorption peaks corresponding to the presence of NH_2 and CN functions. In its ^{1}H NMR spectrum (*DMSO*-d_6) two types of D_2O-exchangeable protons at $\delta = 7.79$ (s, 2H) and 8.32 (s, 2H) ppm corresponding to two NH_2 functions were detected in addition to the aromatic multiplet. The structure of **2** was further confirmed based on its chemical behaviour towards different chemical reagents.

Compounds **2a, b** reacted with CS_2 in the presence of NaH followed by subsequent treatment with an excess of methyl iodide to yield isolable products that could be formulated as 6-amino-2,4-dimethylsulfanylthieno[3,2-*d*]pyrimidine derivatives (**5a, b**). Structure **5** was preferred for such products on the basis of spectroscopic data. Thus, the IR spectrum of **5a**, as an example, revealed the absence of an imine group absorption band. The isomeric thieno[3,2-*d*]thiazine structure **4a** would be expected to exhibit imine group absorption at *ca.* 1700–1670 cm^{-1} [19]. Similar, a *Dimroth* rearrangement has been reported previously [5].

The β-enaminonitrile moiety in **2** proved to be highly reactive. Thus, compound **2a** reacted with an equimolar amount of bromoacetyl bromide in dry dioxane solution under reflux to yield the corresponding 5-amino-3-(α-bromoacetamido)-thiophene derivative **6**. The fact that the reaction took place at the NH_2 group of the β-enaminonitrile moiety rather than at the thiophene C-5 NH_2 group has been proven chemically. Compound **6** in turn reacted with malononitrile in a dioxane solution containing a catalytic amount of Et_3N as HBr acceptor to yield the pyrrolo[1,2-*a*]thieno[2,3-*e*]pyrimidine-6-carbonitrile derivative **8** (Scheme 1). Formation of **8** is assumed to proceed *via* intermediate **7** followed by its subsequent intramolecular cyclization *via* a *Michael* type nucleophilic addition of the NH_2 to the neighbouring thiophene C-2 C≡N function. Structure **8** was established by correct elemental analyses and compatible spectroscopic data. Thus, its IR spectrum (KBr) revealed absorption peaks corresponding to the presence of NH_2, only one CN, and C=O functions.

Compound **2a** added an equimolar amount of trichloroacetonitrile upon boiling under reflux in benzene solution containing a catalytic amount of piperidine to yield the corresponding 4,6-diamino-2-trichloromethylthieno[3,2-*d*]pyrimidine derivative **9**. 4-Aminopyrimidine derivatives have been reported to exhibit a broad spectrum of biological activity [20, 21].

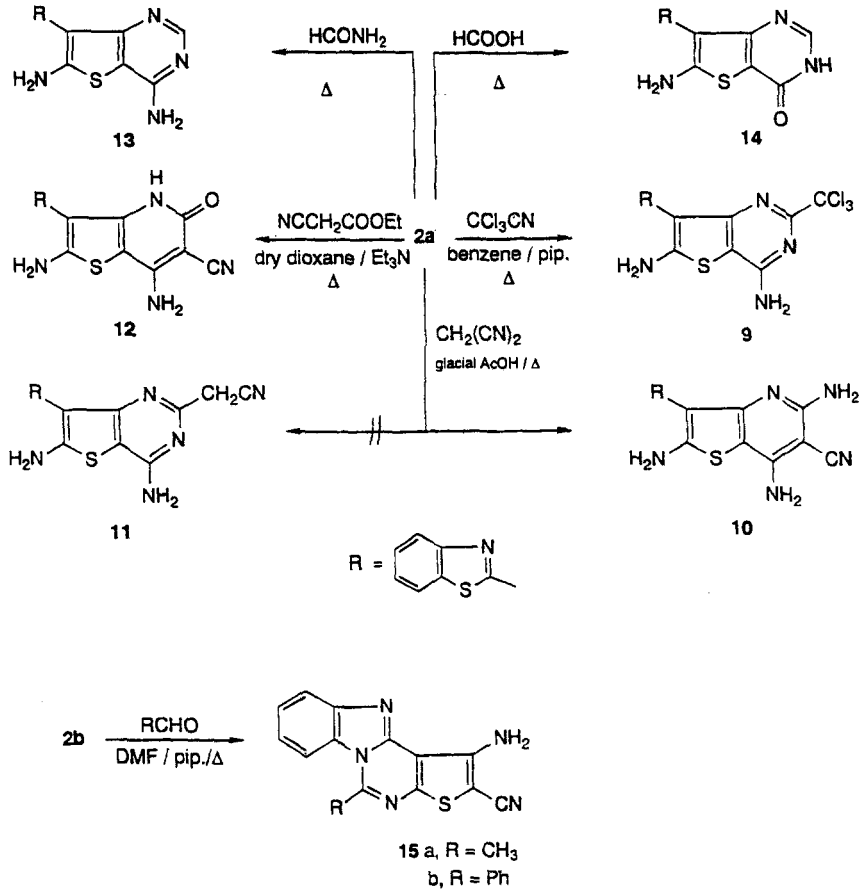
Compound **2a** reacted with malononitrile in glacial AcOH under reflux to yield an 1:1 adduct. Such a product could be formulated as the thieno[3,2-*b*]pyridine derivative **10** or its isomeric thieno[3,2-*d*]pyrimidine derivative **11**.



Scheme 1

Structure **10** was tentatively preferred for this product based on its ^{1}H NMR spectrum which revealed-beside the aromatic multiplet-three types of D_2O-exchangeable protons and the absence of any protons attached to sp^3 carbons.

Likewise, compound **2a** was readily annelated to the corresponding 4,6-diamino-1,2-dihydro-2-oxo-thieno[3,2-*b*]pyridine-3-carbonitrile derivative **12** upon reaction with ethyl cyanoacetate in dry dioxane in the presence of a catalytic amount of Et_3N *via* elimination of EtOH. Upon boiling under reflux with an excess of



Scheme 2

formamide in the presence of formic acid and *DMF*, compound **2a** reacted to yield the corresponding 4,6-diaminothieno[3,2-*d*]pyrimidine derivative **13**. Prolongued heating of **2a** with an excess of formic acid (reflux) afforded the corresponding 6-amino-4-oxo-thieno[3,2-*d*]pyrimidine derivative **14** (Scheme 2). The analytical and spectroscopic data of **13** and **14** are entirely consistent with the proposed structures.

Finally, compound **2b** was readily annelated to the corresponding thieno-[2′,3′:4,5]pyrimido[1,6-*a*]benzimidazole derivatives **15a, b** upon treatment with equimolar amounts of the appropriate aldehyde in refluxing *DMF* containing a catalytic amount of piperidine.

The formation of **15** is believed to proceed *via* loss of a water molecule and subsequent autoxidation involving abstraction of a hydrogen molecule. A similar autoxidation has been reported previously [22–24].

In conclusion, it can be noticed that the results presented indirectly extend and broaden the knowledge in the area of β-enaminonitriles and explore their synthetic

applicability for the construction of polyfunctionally substituted thieno[3,2-*b*]pyridines and thieno[3,2-*d*]pyrimidines obtainable only with difficulty otherwise. Due to the availability of the starting materials, the simplicity of the procedures, and the comparatively reasonable yields of the products, this synthetic approach might be valuable for the synthesis of such ring systems. Investigations on an expansion of this approach to introduce a variety of functional groups in different positions of the basic thieno-pyridine and -pyrimidine structures are in progress.

Experimental

Melting points are uncorrected; IR spectra (KBr): Pye Unicam SP-1000, cm^{-1}; ^1H NMR spectra (*DMSO*-d_6): Varian Gemini 200 MHz spectrometer, *TMS* as internal standard, chemical shifts in δ (ppm); mass spectra: AEI MS 30 mass spectrometer operating at 70 eV; microanalytical data: microanalytical Data Unit at Cairo University. Elemental analyses (C, H, N, S) are in accordance with the calculated values. 2-Cyanomethylbenzothiazole (**1a**) [17] and 2-cyanomethyl-1*H*- benzimidazole (**1b**) [18] were prepared according to the literature.

3,5-Diamino-4-substituted-thiophene-2-carbonitriles (**2a, b**; *general procedure*)

A mixture of **1a, b** (0.01 mol), elemental sulfur (0.32 g, 0.01 mol), and cyanoacetamide (0.84 g, 0.01 mol) in dry *DMF* (40 ml) containing Et_3N (5 drops) was boiled under reflux for 5 h. The reaction mixture was poured into cold H_2O and neutralized with dilute HCl (*pH* = 7). The solid product which precipitated was collected by filtration, washed with water, dried, and crystallized from an appropriate solvent.

4-(Benzothiazol-2-yl)-3,5-diaminothiophene-2-carbonitrile (**2a**)

Yield: 1.74 g (64%); m.p.: 145 °C (dioxane); $C_{12}H_8N_4S_2$ (272.35); IR: 3455–3315 (NH_2), 2223 (CN); ^1H NMR: 7.05–7.38 (m, 4H, arom. protons), 7.79 (s, 2H, NH_2, D_2O-exchangeable), 8.32 (s, 2H, NH_2, D_2O-exchangeable); MS: *m/z* (%) = 272 (M^+, 28%).

4-(Benzimidazol-2-yl)-3,5-diaminothiophene-2-carbonitrile (**2b**)

Yield: 1.55 g (61%); m.p.: 156 °C (dioxane); $C_{12}H_9N_5S$ (255.30); IR: 3470–3300 (NH_2, NH), 2225 (CN); ^1H NMR: 6.95–7.31 (m, 4H, arom. protons), 7.78 (s, 2H, NH_2, D_2O-exchangeable), 8.45 (s, 2H, NH_2, D_2O-exchangeable), 9.93 (s, 1H, NH, D_2O-exchangeable).

6-Amino-2,4-dimethylsulfanylthieno[3,2-d]pyrimidines (**5a, b**; *general procedure*)

To a solution of **2a, b** (0.005 mol) in dry benzene (20 ml) and dry *DMF* (5 ml) containing NaH (0.24 g, 0.01 mol), CS_2 (0.38 g, 0.005 mol) was added. The reaction mixture was refluxed on a boiling water bath for 3 h. After cooling to room temperature, methyl iodide (1.43 g, 0.01 mol) was added and the reaction mixture was refluxed for additional 30 min. The residue obtained on evaporation under vacuum was triturated with EtOH and neutralized with dilute HCl. The solid product formed was filtered off and crystallized from an appropriate solvent.

6-Amino-7-(benzothiazol-2-yl)-2,4-dimethylsulfanylthieno[3,2-d]pyrimidine (**5a**)

Yield: 0.99 g (53%); m.p.: 204 °C (*DMF*); $C_{15}H_{12}N_4S_4$ (376.55); IR: 3455–3310 (NH_2), 860 (SCH_3); ^1H NMR: 3.21 (s, 3H, SCH_3), 3.35 (s, 3H, SCH_3), 6.95–7.33 (m, 4H, arom. protons), 7.95 (s, 2H, NH_2, D_2O-exchangeable).

6-Amino-7-(benzimidazol-2-yl)-2,4-dimethylsulfanylthieno[3,2-d]pyrimidine (**5b**)

Yield: 0.88 g (49%); m.p.: 189 °C (dioxane); $C_{15}H_{13}N_5S_3$ (359.50); IR: 3475–3312 (NH_2, NH), 864 (SCH_3); ^{1}H NMR: 3.12 (s, 3H, SCH_3), 3.33 (s, 3H, SCH_3), 7.02–7.35 (m, 4H, arom. protons), 7.98 (s, 2H, NH_2, D_2O-exchangeable), 8.93 (s, 1H, NH, D_2O-exchangeable).

5-Amino-4-(benzothiazol-2-yl)-3-(α-bromoacetamido)-thiophene-3-carbonitrile (**6**)

To a solution of **2a** (1.36 g, 0.005 mol) in dry dioxane (30 ml), bromoacetyl bromide (1.0 g, 0.005 mol) was added dropwise with stirring at room temperature. The reaction mixture was then boiled under reflux for 30 min, left at room temperature overnight, and poured onto an ice/H_2O mixture. The solid product formed was collected by filtration and crystallized from EtOH.

Yield: 1.04 g (53%); m.p.: 171 °C; $C_{14}H_9BrN_4OS_2$ (393.28); IR: 3473–3310 (NH_2, NH), 2210 (CN), 1700 (CO); ^{1}H NMR: 4.31 (s, 2H, CH_2), 6.53 (s, 2H, NH_2, D_2O-exchangeable), 6.95–7.31 (m, 4H, arom. protons), 8.92 (s, 1H, NH, D_2O-exchangeable).

1-(Benzothiazol-2-yl)-2,4-diamino-7,8-dihydro-8-oxo-pyrrolo[1,2-a]-thieno[2,3-e]pyrimidine-6-carbonitrile (**8**)

To a solution of **6** (1.57 g, 0.004 mol) in dioxane (30 ml) containing a catalytic amount of Et_3N (0.5 ml), malononitrile (0.26 g, 0.004 mol) was added. The reaction mixture was heated under reflux for 3 h, cooled to room temperature, poured onto an ice/H_2O mixture, and neutralized with dilute HCl. The solid product precipitated was collected by filtration, dried, and crystallized from dioxane.

Yield: 0.72 g (48%); m.p.: 198 °C; $C_{17}H_{10}N_6OS_2$ (378.43); IR: 3460–3315 (NH_2), 2215 (CN), 1742 (CO); ^{1}H NMR: 4.23 (s, 2H, CH_2), 6.53 (s, 2H, NH_2, D_2O-exchangeable), 6.95–7.31 (m, 4H, arom. protons), 7.93 (s, 2H, NH_2, D_2O-exchangeable).

7-(Benzothiazol-2-yl)-4,6-diamino-2-trichloromethylthieno[3,2-d]pyrimidine (**9**)

To a solution of **2a** (1.08 g, 0.004 mol) in benzene (30 ml) containing a catalytic amount of piperidine (3 drops), trichloroacetonitrile (0.58 g, 0.004 mol) was added. The reaction mixture was heated under reflux for 4 h and left at room temperature overnight. The mixture was then evaporated *in vacuo*; the residue was triturated with ethanol, collected by filtration, and crystallized from EtOH.
Yield: 0.98 g (59%); m.p.: 185 °C; $C_{14}H_8Cl_3N_5S_2$ (416.74); IR: 3463–3315 (NH_2); ^{1}H NMR: 6.21 (s, 2H, NH_2, D_2O-exchangeable), 7.01–7.35 (m, 4H, arom. protons), 7.93 (s, 2H, NH_2, D_2O-exchangeable).

7-(Benzothiazol-2-yl)-2,4,6-triaminothieno[3,2-b]pyridine-3-carbonitrile (**10**)

To a solution of **2a** (1.36 g, 0.005 mol) in glacial AcOH (30 ml), malononitrile (0.33 g, 0.005 mol) was added. The reaction mixture was heated under reflux for 4 h, cooled to room temperature, and poured onto an ice/H_2O mixture. The solid product precipitated was filtered off, washed several times with water, dried, and crystallized from dioxane.

Yield: 0.86 g (51%); m.p.: 212 °C; $C_{15}H_{10}N_6S_2$ (338.41); IR: 3460–3350 (NH_2), 2218 (CN); ^{1}H NMR: 5.95 (s, 2H, NH_2, D_2O-exchangeable), 6.56 (s, 2H, NH_2, D_2O-exchangeable), 6.95–7.29 (m, 4H, arom. protons), 7.94 (s, 2H, NH_2, D_2O-exchangeable); MS: m/z (%) = 338 (M^+, 18%).

7-(Benzothiazol-2-yl)-4,6-diamino-1,2-dihydro-2-oxo-thieno[3,2-b]pyridine-3-carbonitrile (**12**)

A mixture of **2a** (1.08 g, 0.004 mol) and ethyl cyanoacetate (0.45 g, 0.004 mol) in dry dioxane (30 ml) containing a catalytic amount of Et_3N (3 drops) was heated under reflux for 3 h. The reaction mixture was poured onto cold H_2O. The separated solid product was filtered off and crystallized from dioxane.

Yield: 0.77 g (57%); m.p.: 169 °C; $C_{15}H_9N_5OS_2$ (339.4); IR: 3470–3325 (NH_2, NH), 2215 (CN); 1726 (CO); ^{1}H NMR: 6.21 (s, 2H, NH_2, D_2O-exchangeable), 7.05–7.38 (m, 4H, arom. protons), 8.13 (s, 2H, NH_2, D_2O-exchangeable), 9.36 (s, 1H, NH, D_2O-exchangeable).

7-(Benzothiazol-2-yl)-4,6-diaminothieno[3,2-d]pyrimidine (**13**)

Compound **2a** (1.08 g, 0.004 mol) was heated under reflux with a ternary mixture of formic acid (5 ml), formamide (5 ml), and *DMF* (5 ml) for 10 h. The reaction mixture was then left at room temperature overnight. The solid product formed upon dilution with water was filtered off and crystallized from *DMF*.

Yield: 0.74 g (62%); m.p.: 210 °C; $C_{13}H_9N_5S_2$ (299.38); IR: 3465–3335 (NH_2); ^{1}H NMR: 5.36 (s, 2H, NH_2, D_2O-exchangeable), 6.12 (s, 1H, pyrimidine H-2), 7.05–7.33 (m, 4H, arom. protons), 7.95 (s, 2H, NH_2, D_2O-exchangeable).

6-Amino-7-(benzothiazol-2-yl)-3,4-dihydro-4-oxo-thieno[3,2-d]pyrimidine (**14**)

Compound **2a** (1.08 g, 0.004 mol) was heated under reflux with formic acid (85%, 10 ml) for 12 h. The solid product formed on cooling to room temperature was filtered off and crystallized from *DMF*.

Yield: 0.70 g (59%); m.p.: 169 °C; $C_{13}H_8N_4OS_2$ (300.36); IR: 3475–3310 (NH_2, NH), 1685 (CO); ^{1}H NMR: 6.15 (s, 1H, pyrimidine H-2), 6.98–7.38 (m, 4H, arom. protons), 7.98 (s, 2H, NH_2, D_2O-exchangeable), 9.83 (s, 1H, NH, D_2O-exchangeable).

Thieno[2',3':4,5]pyrimido[1,6-a]benzimidazoles (**15a, b**; *general procedure*)

To a solution of **2b** (1.02 g, 0.004 mol) in *DMF* (30 ml) containing a catalytic amount of piperidine (3 drops), the appropriate aldehyde (0.004 mol) was added. The reaction mixture was heated under reflux for 6 h, poured into an ice/H_2O mixture (30 ml), and neutralized with dilute HCl. The solid product was filtered off and crystallized from an appropriate solvent.

15a: Yield: 0.51 g (46%); m.p.: 188 °C (dioxane); $C_{14}H_9N_5S$ (279.32); IR: 3450–3320 (NH_2), 2220 (CN); ^{1}H NMR: 2.31 (s, 3H, CH_3), 6.95–7.31 (m, 4H, arom. protons), 8.83 (s, 2H, NH_2, D_2O-exchangeable); MS: m/z (%) = 279 (M^+, 21%).

15b: Yield: 0.69 g (51%); m.p.: 216 °C (dioxane); $C_{19}H_{11}N_5S$ (341.39); IR: 3445–3324 (NH_2), 2218 (CN); ^{1}H NMR: 6.85–7.41 (m, 9H, arom. protons), 7.84 (s, 2H, NH_2, D_2O-exchangeable).

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