ALTERNATIVE PRODUCTS IN ONE-POT REACTION OF BENZYLIDENE-MALONONITRILE, THIOCARBAMOYLACETAMIDE AND HALOMETHYL KETONES

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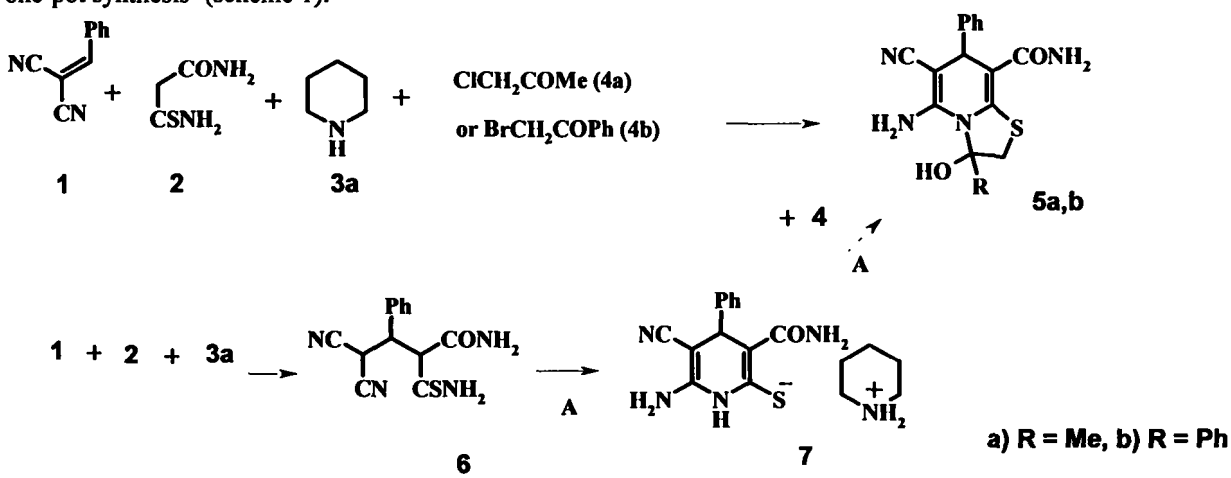
Abstract: 6-Oxo-5-(1,3-thiazol-2-yl)-1,4,5,6-tetrahydropyridine-3-carbonitriles **17**, corresponding 6-oxo-5-(1,3-thiazol-2-yl)-5,6-dihydropyridine-3-carbonitriles **18** and intermediates - 2-(1,3-thiazol-2-yl)acetamides **15** and 4,4-dicyano-2-(1,3-thiazol-2-yl)-butyramides **16** have been obtained as alternative products to 3-hydroxy-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines **5** carrying out one-pot condensation of 2-thiocarbamoylacetamide **2**, base **3**, halomethyl ketones **4** and benzylidenemalononitrile **1**.

Introduction

It was shown that 3-hydroxy-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines **5** have been obtained in 84 – 90 % yields by condensation of benzylidenemalononitrile **1**, 2-thiocarbamoylacetamide **2**, piperidine **3a** and halomethyl ketones **4** in a one-pot synthesis[1] (scheme 1).



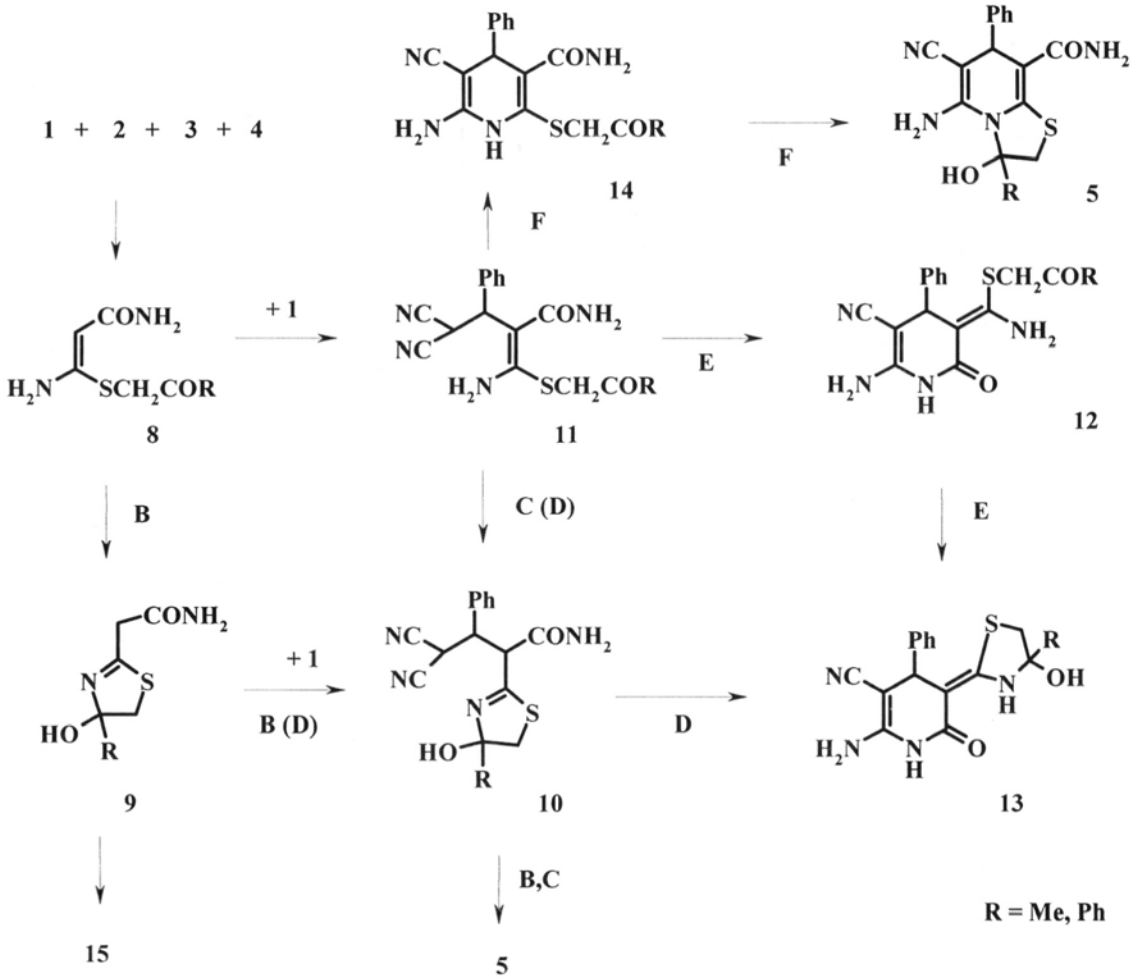
Scheme 1

The isolated intermediate – thiolate **7**[2] (reaction **1** + **2** + **3**, yield 85 %) and quantitative formation of **5** by treatment of **7** with **4**[1] demonstrate that by making use of sequence **1** + **2** + **3** + **4** the Michael addition takes place in the first stage yielding 4,4-dicyanothiobutyroamide **6** which easily undergoes intramolecular cyclization, alkylation and another intramolecular cyclization to give **5** (path **A**). It should be noted, firstly, that the intramolecular cyclizations of 4-keto(cyano)semithiobutyrodiamides (of type **6**) giving rise to 2-oxo-3-thiocarbamoyl-1,2,3,4-tetrahydropyridines[3,4] or

3-carbamoyl-2-thioxo-1,2,3,4-tetrahydropyridines[1,5,6] are competing reactions, and, secondly, that the substituents and the reaction conditions significantly influence the formed products.

Theoretically, alternative paths **B** - **F** leading to 5-[amino(alkylsulfanyl)methylene]-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **12** and 6-oxo-5-thiazolidin-2-ylidene-1,4,5,6-tetrahydropyridine-3-carbonitriles **13** with the same molecular formula as thiazolo[3,2-*a*]pyridines **5** are possible (Scheme 2).

If alkylation of 2-thiocarbamoylacetamide **2** (soft nucleophile) proceeds first to give 3-amino-3-alkylthioacrylamides **8**, then in the next step there are five main possibilities. The formation of 2-(4-hydroxy-4-R-4,5-dihydro-1,3-thiazol-2-



Scheme 2

yl)acetamides **9** by intramolecular cyclization of acrylamide **8**, the Michael reaction of **1** and **9** could give thiazolylbutyramides **10** and further **5** (path **B**). Compound **5** could be obtained also from **10** via the formation of 2-[amino(alkylsulfanyl)methylene]butyramide **11** (from **1** and **8**) and with subsequent transformation of **11** to **10** (path **C**). So, thiazolylbutyramides **10** could be formed both through intermediates **9** or **11**. In both cases 4-cyano and 2-thiazolyl groups of butyramide **10** are involved in the intramolecular cyclization. Alternative intramolecular cyclization of 4-cyano group and carbamoyl group of butyramide **10** could give 6-oxo-5-thiazolidin-2-ylidene-1,4,5,6-tetrahydropyridine-3-carbonitriles **13** (path **D**). The path **E** leading to **13** through **11** and **12** and path **F** (competing to path **A**) leading to **5** through **11** and 2-carbonylmethylsulfanyl-1,4-dihydropyridines **14** are also possible.

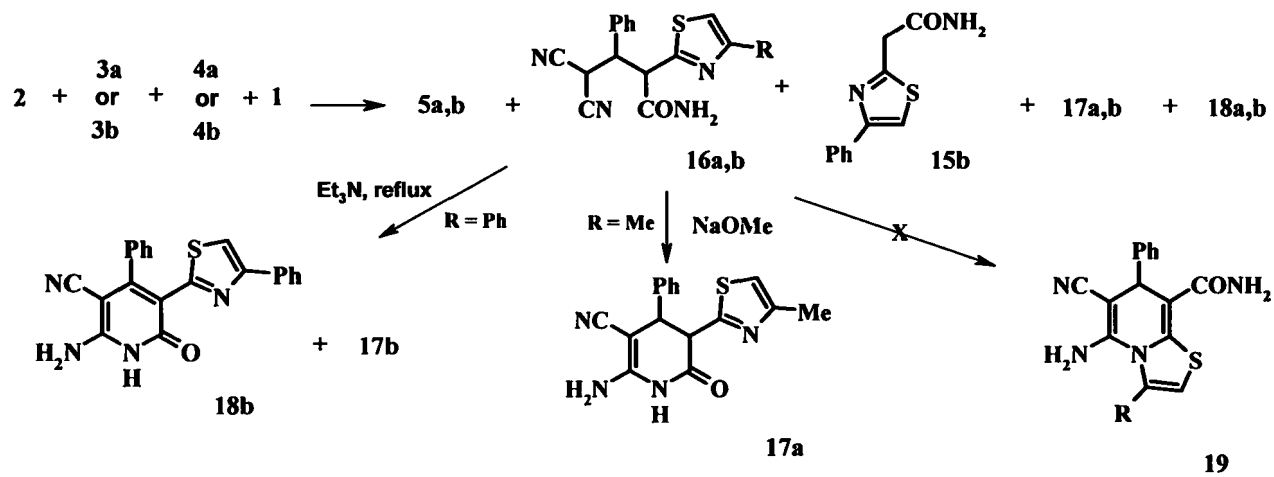
Results and discussion

The sequence of compounds [**1** + **2** + **3a** + **4**] is important for reaching 84-90% yield of 3-hydroxy-2,3-dihydro-7H-thiazolo[3,2-a]pyridines **5**[1]. In the continuing investigation of this effective one-pot synthesis, which proceeds at very mild conditions, we tried to answer, if alternative paths **B** - **F** take place. By changing the above mentioned sequence of addition of reagents and the reaction conditions we tried to obtain and separate intermediates **8** – **11**, 6-oxopyridine-3-carbonitriles **12** and **13**, and to carry out stepwise synthesis of them.

The sequence [**2** + **4** + **3** + **1**], which used similar reaction conditions as for the preparation of **5** as well as at elevated reaction temperature, gives rise to a mixture of thiazolopyridines **5**, 2-(1,3-thiazol-2-yl)acetamides **15**, 4,4-dicyano-2-(1,3-thiazol-2-yl)butyramides **16**, 5-(1,3-thiazol-2-yl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **17**, corresponding 5-(1,3-thiazol-2-yl)-6-oxo-5,6-dihydropyridine-3-carbonitriles **18** and several unidentified products (Scheme 3). The use of triethylamine **3b** instead of piperidine **3a** and maintaining reaction temperature under 50 °C gave slightly simpler reaction mixture.

In case of the sequence [**2** + **4a** + **3b** + **1**], on short heating till 30 – 40 °C, from the reaction mixture are isolated 9 % of **5a**, 14 % of **16a** and 3 % of **17a** by fractional crystallization. By treatment of **16a** with sodium methylate **3c** (short heating with subsequent stirring) 33 % of **17a** are obtained. In case of sequence [**2** + **4b** + **3b** + **1**] from the reaction mixture containing **5** and **15** – **18** (TLC) 12 % of **5b** and 60 % of **15b** are isolated.

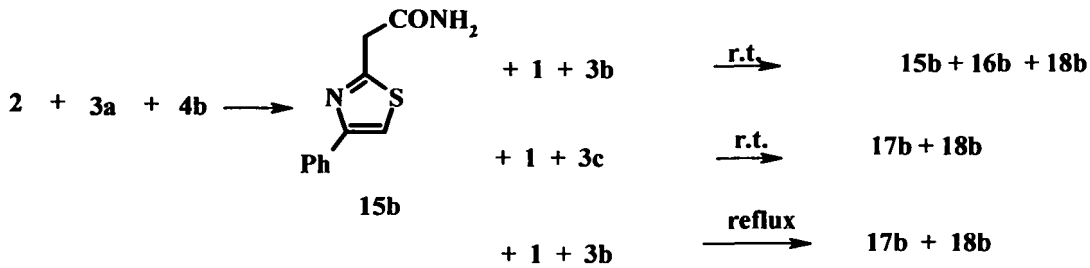
By refluxing the mixtures [**2** + **4a** + **1**] and [**2** + **4b** + **1**] both with **3a** and **3b** leads to inseparable reaction mixtures. It is worth mentioning that 2-(1,3-thiazol-2-yl)acetamide **15b**[7] forms at similar reaction conditions used for the preparation of thiazolo[3,2-a]pyridine **5b**[1]. By carrying out gradual synthesis, we did not succeed in isolating intermediate of **15b** - 2-(4'-hydroxy-4',5'-dihydro-1',3'-thiazolyl)acetamide **9b** even at lower temperature.



Scheme 3

These experiments demonstrate that two alternative paths, **A** and modified **B**, could be taken into consideration. The presence of products **16** – **18** in reaction mixture is explained by formation of 2-(1,3-thiazolyl)acetamides **15** (reaction **2** + **4**, isolated in case R = Ph) competitively to 4,4-dicyanothiobutyroamide **6** (reaction **1** + **2**) in the first stage.

As 2-(1,3-thiazolyl)acetamide **15b** was isolated as main product applying sequence [**2** + **4b** + **3b** + **1**], we carried out Michael reaction of **15b** with **1** trying to raise the yields of products **16** – **18**.



By cyclocondensation of [**15b** + **3b** + **1**] (room temperature, 3 days stirring) next to 33 % of unreacted **15b**, 47 % of **16b** and 2 % of **18b** are isolated. When sodium methylate **3c** was used instead of **3b**, 10 % of **17b** and 19 % of **18b** were isolated. The 7 h refluxing of [**15b** + **3b** + **1**] gave rise to 56 % of **17b** and 7 % of **18b**.

Refluxing of **16b** for 2 h in the presence of triethylamine **3b** gave rise to 59 % of **17b** and 5 % of **18b**. It is worth to mention that no trace of thiazolo[3,2-a]pyridines **19** has been isolated. The use of column chromatography is complicated due to instability of compounds **16** and **17** and very close R_f values of compounds of type **16 – 18.**

The structures of compounds **15 – 18** are proved by spectroscopic methods. In case of **16a,b** the IR spectra band for $\nu_{C\equiv N}$ at 2256 – 2258 cm^{-1} shows that cyano group is connected with sp^3 hybridised carbon atom. In the ^1H NMR spectra of **16a,b** a characteristic three adjacent proton system is observed. In the IR spectra of **17a,b** absorption band for $\nu_{C\equiv N}$ is at 2195 – 2200 cm^{-1}, but for **18b** is seen at 2218 cm^{-1}. In the ^1H NMR spectra of **17a,b** characteristic doublets ($J_{4,5}$ = 5.2 – 6.0 Hz) of H_4 and H_5 protons are observed. In case of the alternative structure **19** a singlet of H_4 should be observed at 4.5 – 4.6 ppm[4].

In conclusion, the investigation of one-pot cyclocondensation of benzylidenemalononitrile **1**, 2-thiocarbamoylacetamide **2**, base **3** and alkyl halides **4** showed, that only in the case when sequence of the reagents [**1** + **2** + **3** + **4**] was maintained at reaction temperature under 30 °C, a high yield formation of 3-hydroxy-2,3-dihydro-7*H*-thiazolo[3,2-a]pyridines **5** was observed.

In case of sequence [**2** + **4** + **3** + **1**] besides 7*H*-thiazolo[3,2-a]pyridines **5**, alternate products corresponding to 3-(1,3-thiazol-2-yl)-3,4-dihydropyridin-2(1H)-ones **17**, pyridin-2(1H)-ones **18** and intermediates - 2-(1,3-thiazol-2-yl)acetamides **15** and 4,4-dicyano-2-(1,3-thiazol-2-yl)butyramides **16** were obtained.

The crucial steps determining the formation of alternative products (different molecular formula) were competitive Michael reaction of **1** and **2** and the formation of thiazolylacetamide **15** by alkylation of **2** with **4**. In comparison with the stable 3-hydroxy-2,3-dihydro-7*H*-thiazolo[3,2-a]pyridines **5**, monocyclic 4-hydroxy-4,5-dihydro-1,3-thiazoles **9** even under mild reaction conditions appeared to be unstable compounds. Their easy transformation to thiazolylacetamides **15** exclude the alternative path leading to **5** or 6-oxo-5-thiazolidin-2-ylidene-1,4,5,6-tetrahydropyridine-3-carbonitriles **13** with equal molecular formula.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. The IR spectra of suspensions of the compounds in mineral oil were recorded (ν,cm^{-1}) with a Perkin-Elmer 580 B spectrometer. The ^1H NMR spectra of solutions in $CDCl_3$ or DMSO-d_6 were obtained with a Bruker WH 90/DC (90 MHz) and AM-360 (360 MHz) spectrometers. Chemical shifts were expressed in δ downfield from TMS and coupling constants (J) in Hertz. The course of the reactions and the purity of the substances were monitored by TLC on Kieselgel 60 F Merck plates with dichloromethane-hexane-methanol (5:5:1) as eluent. Compounds were recrystallized from EtOH. The compound **15b** was synthesized as described[8].

Cyclocondensation of [2 + 4a+ 3b + 1].

A mixture of 2-thiocarbamoylacetamide **2a** (1.18g,10 mmol), chloroacetone **4a** (0.9 ml, 10.7 mmol) and triethylamine **3b** (1.4 ml, 10 mmol) in 10 ml of ethanol was stirred at room temperature for 10 min. A warm solution of benzylidenemalononitrile **1** (1.54 g, 10 mmol) in 10 ml of ethanol was added and reaction mixture was stirred at ambient temperature for 30 min. The precipitated crystals were removed by filtration, washed with 5 ml of water to give 0.22 g (6.7%) of **5a** as colourless crystals, mp 216 – 218 ^{o}C.[2] After 20 h 2.10 g of crude product was separated by filtration. By recrystallization from ethanol first 0.07 g (2.1 %) of **5a** was separated by filtration, then 0.42 g (13.5 %) of **4,4-dicyano-2-(4-methyl-1,3-thiazol-2-yl)-3-phenylbutyramide (16a)** as colourless crystals was isolated, mp 132-134 °C; IR: 3450, 3314, 3200 (NH); 2258 (C≡N); 1700, 1676 (C=O); ^{1}H NMR (DMSO-d_6,): 2.45 (3H, s, 4'-CH_3); 4.02 (1H, dd, J = 4.5 and 12.0 Hz, 3-H); 4.82 (1H, d, J = 12.0 Hz, 2-H); 4.97 (1H, d, J = 4.5 Hz, 4-H); 7.32 (1H, s, 5'-H); 7.06 and 7.88 (2H, 2s, $CONH_2$); 7.4 - 7.6 (5H, m, C_6H_5); Anal.Calcd. for $C_{16}H_{14}N_4OS$ x 0.5H_2O: C 60.17, H 4.73, N 17.54, S 10.04; Found: C 60.01, H 4.82, N 17.39, S 10.00. After concentration of the remaining filtrate (kept for 3 days) at half of the initial volume, 0.1 g (3 %) of **17a** as yellow crystals was separated by filtration, mp > 160^{o}C (decomp.); IR: 3390, 3336, 3222 (NH, NH_2); 2200 (C≡N); 1708, 1667 (C=O); ^{1}H NMR (DMSO-d_6): 2.33 (3H, s, 4'-CH_3); 4.12 (1H, d, J = 5.2 Hz, 5-H); 4.26 (1H, d, J = 5.2 Hz, 4-H); 6.17 (2H, s, 6-NH_2); 7.20 (1H, s, 5'-H); 7.2 - 7.7 (5H, s, 4-C_6H_5); 10.06 (1H, s, NH); Anal. Calcd. for $C_{16}H_{14}N_4OS$: C 61.92, H 4.55, N 18.05, S 10.33; Found: C 62.16, H 4.39, N 17.86, S 9.97.

2-Amino-5-(4-methyl-1,3-thiazol-2-yl)-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (17a).

A mixture of butyramide **16a** (0.09 g, 0.3 mmol) and 0.2 ml 2N MeONa **3c** in 3 ml of methanol was shortly heated till dissolution and stirred at ambient temperature for 30 min. Then 0.1 ml of acetic acid and 2 ml of water were added. After 3 h the precipitated crystals were removed by filtration to give 0.03 g (33 %) of **17a**.

Cyclocondensation of [2 + 4b+ 3b + 1].

A mixture of 2-thiocarbamoylacetamide **2** (1.18g,10 mmol), bromoacetophenone **4b** (2.2 g, 11 mmol) and triethylamine **3b** (1.4 ml, 10 mmol) in 15 ml of ethanol was stirred at room temperature for 10 min. A warm solution of benzylidenemalononitrile **1** (1.54 g, 10 mmol) in 10 ml of ethanol was added and the reaction mixture was stirred at ambient temperature for 10 min. The precipitated crystals were removed by filtration to yield 0.47 g (12 %) of thiazolo[3,2-a]pyridine **5b** as colourless crystals, m.p. 190 – 192 ^{o}C[1]. The remaining filtrate was cooled to 0 ^{o}C and the precipitate was filtered to give 1.31 g (60 %) of 2-(4-phenyl-1,3-thiazol-2-yl)acetamide (**15b**) as grey crystals, mp 185 – 186 ^{o}C[7].

Cyclocondensation of [15b + 3b + 1].

1. A mixture of thiazolylacetamide **15b** (0.65 g, 3 mmol) and benzylidenemalononitrile **1** (0.46 g, 3 mmol) in 25 ml of ethanol was shortly heated till dissolution and 0.5 ml of triethylamine **3b** was added and stirred at ambient temperature for 6 h. The precipitated crystals were separated to give 0.22 g (33 %) of **15b**. From the filtrate after 20 h the precipitated crystals were separated to give 0.02 g (2 %) of **2-amino-6-oxo-4-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,6-dihydropyridine-3-carbonitrile (18b)** as yellow crystals, mp 268 - 270 °C; IR: 3320, 3214, 3190 (NH, NH_2); 2218 (C≡N); 1654 (C=O); ^{1}H NMR (DMSO-d_6): 7.2 - 7.5 (12H, complex, 2 C_6H_5 and NH_2); 7.80 (1H, s, 5'-H); 11.76 (1H, s, NH); Anal. Calcd. for $C_{21}H_{14}N_4OS$ x 0.5 H_2O: C 66.47, H 3.98, N 14.77, S 8.45; Found: C 66.84, H 4.18, N 14.51, S 8.32. The remaining solution was poured into 100 ml of water. The precipitate was filtered and dissolved in 15 ml of ethanol. The precipitated crystals were separated during 2 days to give 0.52 g (47 %) of **4,4-dicyano-3-phenyl-2-(4-phenyl-1,3-thiazol-2-yl)-butyramide (16b)** as colourless crystals, mp 131-132 °C; IR: 3458, 3340 (NH_2); 2256 (C≡N); 1688, 1673 (C=O); ^{1}H NMR (DMSO-d_6): 4.08 (1H, dd, J = 4.1 and 12.0 Hz, 3-H); 4.97 (1H, d, J = 12.0 Hz, 2-H); 5.05

(1H, d, J = 4.1 Hz, 4-H); 7.3 - 8.0 (10H, complex, 2 C_6H_5); 7.17 and 8.08 (2H, 2s, 3-$CONH_2$); 7.40 (1H, s, 5'-H); Anal. Calcd. for $C_{21}H_{16}N_4OS$: C 67.72, H 4.33, N 15.04, S 8.61; Found: C 67.67, H 4.30, N 15.16, S 8.60.

2. A mixture of thiazolylacetamide **15b** (1.09 g, 5 mmol), benzylidenemalononitrile **1** (0.77 g, 5 mmol) and triethylamine **3b** (0.7 ml, 5 mmol) in 20 ml of ethanol was refluxed for 7 h and stirred at room temperature for 20 h. The precipitated crystals were separated by filtration to give 1.05 g (56 %) of **2-amino-6-oxo-4-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,4,5,6-tetrahydropyridine-3-carbonitrile 17b** as yellow crystals, mp 236 – 238 °C; IR: 3430, 3322, 3204 (NH, NH_2); 2195 (C≡N); 1714, 1654 (C=O); ^{1}H NMR (DMSO-d_6): 4.28 (1H, d, J = 6.0 Hz, 5-H), 4.46 (1H, d, J = 6.0 Hz, 4-H); 6.20 (2H, s, 6-NH_2); 7.2 - 8.0 (10H, m, 2 C_6H_5); 8.02 (1H, s, 5'-H); 10.14 (1H, s, NH); Anal.Calcd. for $C_{21}H_{16}N_4OS$: C 67.72, H 4.33, N 15.04, S 8.61; Found: C 67.43, H 4.38, N 14.93, S 8.72. The crystals precipitated from filtrate after 20 h were separated to give 0.06 g (3 %) of 6-oxo-1,6-dihydropyridine-3-carbonitrile **18b**.

Cyclization of 16b with triethylamine 3b.

A mixture of 4,4-dicyano-2-thiazolylbutyramide **16b** (0.19 g, 0.5 mmol) and triethylamine **3b** (0.1 ml, 0.7 mmol) in 5 ml of ethanol was refluxed for 2 h and stirred at room temperature for 1 h. The precipitated crystals were separated by filtration to give 0.11 g (59 %) of 6-oxo-5-thiazolyl-1,4,5,6-tetrahydropyridine-3-carbonitrile **17b**. The crystals precipitated from filtrate after 20 h were separated to give 0.01 g (5 %) of 6-oxo-1,6-dihydropyridine-3-carbonitrile **18b**.

Cyclocondensation of [15b + 3c+ 1].

A mixture of thiazolylacetamide **15b** (1.09 g, 5 mmol), benzylidenemalononitrile **1** (0.77 g, 5 mmol) and 10 ml of 2N NaOMe **3c** in 40 ml of methanol was stirred at room temperature for 3 h. The precipitated crystals were separated by filtration to give 0.19 g (10 %) of 6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile **17b**. From the remaining filtrate (kept at room temperature for 60 h) additional crystals were separated by filtration to give 0.35 g (19 %) of 6-oxo-1,6-dihydropyridine-3-carbonitrile **18b**.

REFERENCES

1. A. Krauze, J. Popelis, G. Duburs Tetrahedron **54**, 9161 (1998).
2. A. Krauze, J. Popelis, G. Duburs Heterocyclic Commun.**3**, 515 (1997).
3. K.U. Sadek, A.E. Mourad, A.E. Abd-Elhaheez, M.H. Elnagdi Synthesis 739 (1983).
4. A.A. Krauze, E.E. Liepinsh, G.Ya. Dubur Chem. Heterocycl. Comp. **25**, 650 (1989).
5. L.A. Rodinovskaya, A.M. Shestopalov, V.N.Nesterov Chem. Heterocycl. Comp. **32**, 1182 (1996).
6. S.H. Hussain, S.M. Sherif, M.M. Youssef Gazz.Chim.Ital. **124**, 97 (1994).
7. A.M. El-Reedy, S.M. Hussain, M.M.M.Youssef J. prakt. Chem. **330**, 521 (1988).

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