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ALTERNATIVE PRODUCTS IN ONE-POT REACTION OF BENZYLIDENE-MALONONITRILE, N-METHYL-2-THIOCARBAMOYLACETAMIDE, AND ω-BROMOACETOPHENONE

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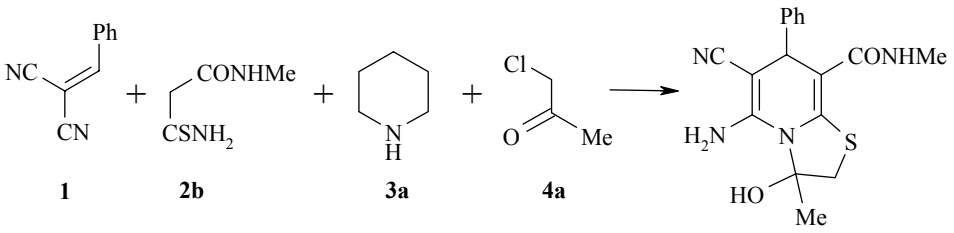
N-Methyl-2-benzoylmethylsulfanyl-4-phenylnicotinamide and N-methyl-2-(4-phenyl-1,3-thiazol-2-yl)-acetamide have been obtained as alternative products to the desired N-methyl-2,3-dihydro-7H-thiazolo[3,2-a]pyridine-8-carboxamide by a one-pot cyclocondensation of benzylidenemalononitrile, N-methyl-2-thiocarbamoylacetamide, piperidine, and ω-bromoacetophenone. 2-Amino-1-methyl-6-oxo-4-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,6-dihydropyridine-3-carbonitrile has been obtained as main product by treatment of benzylidenemalononitrile with N-methyl-2-(1,3-thiazol-2-yl)acetamide.

Keywords: 2-(benzoylmethylsulfanyl)nicotinamide, 2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxamide, N-methyl-2-(1,3-thiazol-2-yl)acetamide, 6-oxo-5-(thiazol-2-yl)-1,6-dihydropyridine-3-carbonitrile.

Previously it was established that the *one-pot* condensation of benzylidenemalononitrile (**1**), N-methyl-2-thiocarbamoylacetamide (**2b**), piperidine **3a**, and chloroacetone **4a** resulted in N-methyl-3-hydroxy-3-methyl-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxamide (**5**) obtained in 82% yield (Scheme 1) [1].

It was also proved that N-unsubstituted 3-hydroxy-3-phenyl-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxamide (**6a**) can be prepared both by the above mentioned *one-pot* multicomponent synthesis (yield 84%) [1] or by treatment of 1,4-dihydropyridine-6-thiolate **8a** [2] with ω-bromoacetophenone **4b** (yield 83%) [1].

Scheme 1



1 **2b** **3a** **4a** **5**

* Dedicated to Professor I. Kalvinsh on his 60th birthday

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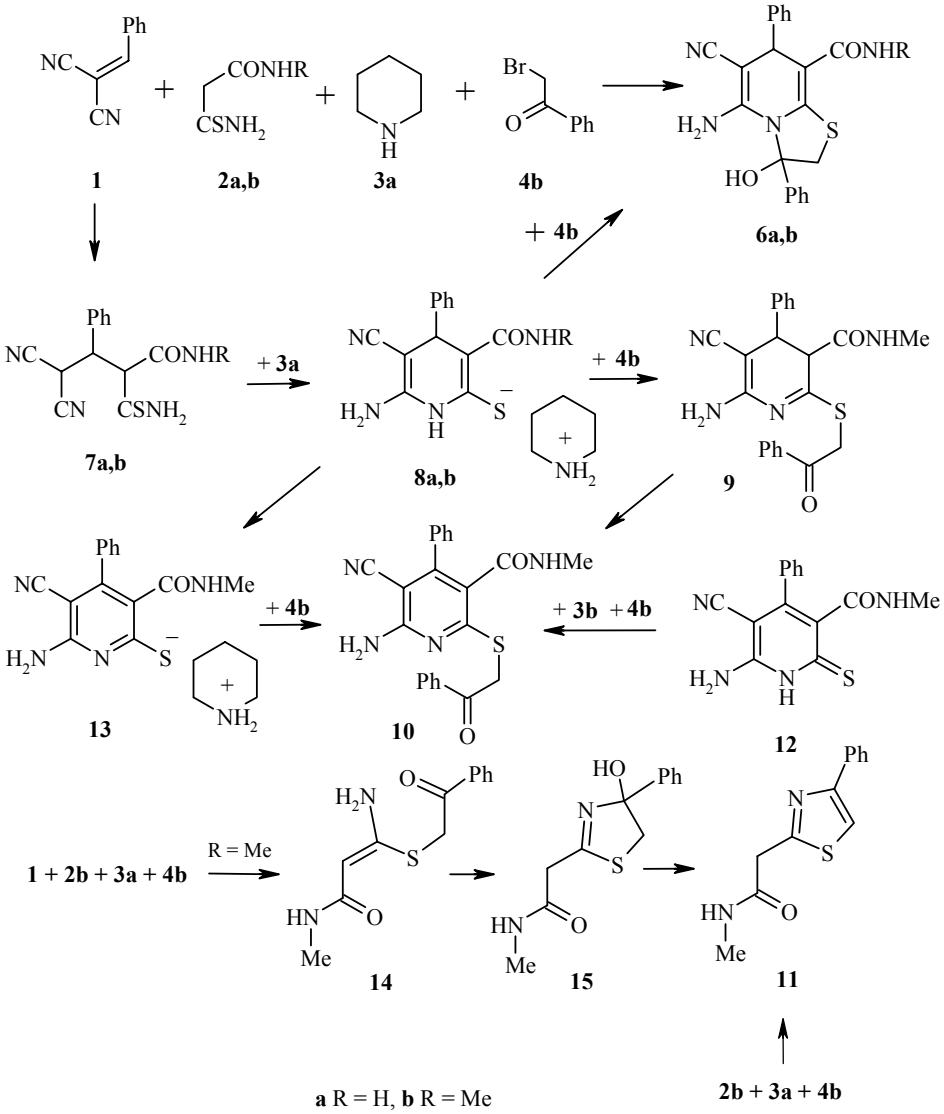
The mechanism for the formation of the thiazolo[3,2-*a*]pyridine-8-carboxamides **5** and **6a** is as follows: in the first stage the Michael addition of 2-thiocarbamoylacetamide **2** to benzylidenemalononitrile **1** affords 4,4-dicyanothiobutyramides of type **7**, which easily undergo intramolecular cyclization producing thiolates **8** [2]. Then alkylation of **8** and another intramolecular cyclization occur to give thiazolo[3,2-*a*]pyridine-8-carboxamides **5** and **6**. It should be noted, firstly, that the intramolecular cyclizations of Michael adducts like **7**, which produce 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 structure of the products formed.

Our efforts to obtain the analog of **5**, N-methyl-5-amino-6-cyano-3-hydroxy-3,7-diphenyl-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxamide (**6b**) by condensation of benzylidenemalononitrile **1**, N-methyl-2-thiocarbamoylacetamide **2b**, piperidine **3a**, and bromoacetophenone **4b** (in a similar manner as for **6a)** were unsuccessful. The isolated products (Scheme 2) were N-methyl-6-amino-2-benzoylmethylsulfanyl-5-cyano-4-phenylnicotinamide (**10**) and N-methyl-2-(4-phenyl-1,3-thiazol-2-yl)acetamide (**11**).

Scheme 2



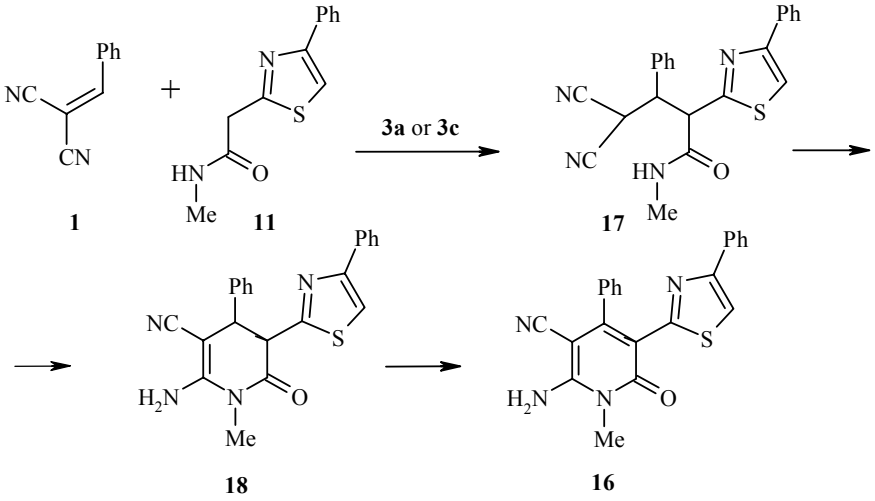
The formation of alternative products **10** and **11** can be explained as follows. Under mild reaction conditions two competing reactions take place. First, the Michael addition of N-methyl-2-thiocarbamoylacetamide (**2b**) to compound **1** affords 4,4-dicyanothiobutyramide **7b**, which further through thiolate **8b** and 2-benzoylmethylsulfanyl-3,4-dihydronicotinamide **9** produces 2-(benzoylmethyl-sulfanyl)nicotinamide **10**. The alternative path, *i. e*. oxidation of 1,4-dihydropyridine-2-thiolate **8b** to pyridine-2-thiolate **13** and its alkylation with bromoacetophenone **4b** yielding pyridine **10**, also cannot be excluded. In both cases, benzylidenemalononitrile **1** could act as oxidizing agent, which in turn could diminish yields of the products. Secondly, due to alkylation of N-methyl-2-thiocarbamoylacetamide **2b** (soft nucleophile) with bromoacetophenone **4b**, 3-amino-3-alkylthioacrylamide **14** forms, which by intramolecular acylation yields N-methyl-2-(4-hydroxy-4-phenyl-4,5-dihydro-1,3-thiazol-2-yl)acetamide **15**, which, in turn, after dehydration produces N-methyl-2-(4-phenyl-1,3-thiazol- 2-yl)acetamide (**11**).

As the sterically smaller 7H-thiazolo[3,2-*a*]pyridines **5** and **6a** were obtained in high yields, an explanation for the difference in the case of the desired **6b** could be the following: due to steric reasons the intramolecular acylation of N-methyl-2-benzoylmethylsulfanyl-3,4-dihydronicotinamide (**9**), obviously, proceeds slower and competing oxidation takes place to form pyridine **10**. Compound **10** was prepared also by alkylation of thione **12** [2] with **4b** in the presence of triethylamine (**3b**).

N-Methyl-2-(4-phenyl-1,3-thiazol-2-yl)acetamide (**11**) was obtained also by treatment of compound **2b** with bromoacetophenone **4b** in the presence of piperidine **3a**.

Treatment of compound **11** with nitrile **1** at room temperature yielded 2-amino-1-methyl-6-oxo-4-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,6-dihydropyridine-3-carbonitrile (**16**) as the main product applying either piperidine **3a** or NaOMe (**3c**) as a base (Scheme 3). Refluxing of the above-mentioned reagents (**1** and **11** plus **3a** or **3c**) leads to complicated inseparable reaction mixtures. The formation of **16** can be explained as follows. First, the Michael addition of **11** to **1** takes place to form adduct **17**, which further intramolecularly cyclizes and oxidizes.

Scheme 3



The structures of compounds **10**, **11**, and **16** have been proved by spectroscopic methods. In the case of **10** the characteristic bands for $\nu_{C=O}$ and $\nu_{C\equiv N}$ are observed in the IR spectrum. In the ^{1}H NMR spectra of compounds **10** and **11**, contrary to **16**, the characteristic doublets (J = 4.5–4.6 Hz) of NH$\underline{CH_3}$ protons are observed.

To conclude**,** the investigation of a *one-pot* cyclocondensation of benzylidenemalononitrile **1**, N-methyl-2-thiocarbamoylacetamide **2b**, piperidine **3a**, and bromoacetophenone **4b** showed that instead of the desired N-methyl-2,3-dihydro-7H-thiazolo[3,2-*a*]pyridine-8-carboxamide (**6b**), N-methyl-2-benzoylmethylsulfanyl-4-phenylnicotin-amide (**10)**, and N-methyl-2-(4-phenyl-1,3-thiazol-2-yl)acet- amide (**11**) were formed.

The formation of alternative products **10** and **11** was determined by competitive Michael reaction of **1** and compound **2b** and alkylation of **2b** with compound **4b**, which proceeded under similar reaction conditions**.**

Formation of **10** instead of **6b** is explained by steric reasons. Due to them, the intramolecular acylation of N-methyl-2-benzoylmethylsulfanyl-3,4-dihydronicotinamide **9**, obviously, proceeded slower and a competing oxidation took place to form **10**.

Easily proceeding cascade reactions by alkylation of **2b** with compound **4b** led to stable compound **11.** By treatment of **11** with compound **1** under mild reaction conditions, another cascade reaction took place, yielding 1-methyl-6-oxo-5-(1,3-thiazol-2-yl)-1,6-dihydropyridine-3-carbonitrile **16**.

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 were obtained with a Bruker WH 90/DC (90 MHz) spectrometer. Chemical shifts were expressed downfield from TMS. 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.

N-Methyl-6-amino-2-benzoylmethylsulfanyl-5-cyano-4-phenylnicotinamide (**10).** A mixture of thione **12** [2] (0.57 g, 1 mmol), triethylamine **3b** (0.28 ml, 2 mmol), and bromoacetophenone **4b** (0.4 g, 2 mmol) in ethanol (10 ml) was refluxed for 5 min and stirred at room temperature for 1 h. Then the precipitate was filtered off and washed with ethanol (2 ml) and water (5 ml) to give nicotinamide **10** (0.66 g, 82%) as yellow crystals, mp 218-220°C. IR spectrum, ν, cm^{-1}: 3460, 3300, 3204 (NH, NH_2); 2205 (C≡N); 1698, 1640 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.42 (3H, d, *J* = 4.5, NH$\underline{CH_3}$); 4.86 (2H, s, SCH_2); 6.96 (2H, s, NH_2); 7.2-8.2 (11H, m, $\underline{NH}CH_3$, $2C_6H_5$). Found, %: C 64.69; H 4.33; N 13.61; S 7.87. $C_{22}H_{18}N_4O_2S$. Calculated, %: C 65.65; H 4.51; N 13.92; S 7.97.

N-Methyl-2-(4-phenyl-1,3-thiazol-2-yl)acetamide (**11**)**.** A mixture of N-methylthiocarbamoylacetamide (**2b**) (2.64 g, 20 mmol), ω-bromoacetophenone **4b** (4.4 g, 21 mmol), and piperidine **3a** (1 ml, 10 mmol) in ethanol (25 ml) was heated till dissolution and filtered, and gradually of water (10 ml) was added. After 2 h the precipitate was removed by filtration to give **11** (4.40 g, 94%) as colorless crystals, mp 118-120°C. IR spectrum, ν, cm^{-1}: 3280 (N–H); 1640 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.86 (3H, d, *J* = 4.6, NH$\underline{CH_3}$); 3.92 (2H, s, CH_2); 7.18 (1H, q, *J* = 4.6, $\underline{NH}CH_3$); 7.42 (1H, s, H-5); 7.3–7.9 (5H, m, 4-C_6H_5). Found, %: C 61.86; H 5.17; N 11.83; S 13.62. $C_{12}H_{12}N_2OS$. Calculated, %: C 62.04; H 5.21; N 12.06; S 13.80.

Cyclocondensation of [1 + 2b + 3a + 4b]. A. A mixture of compounds **1** (0.77 g, 5 mmol), **2b** (0.66 g, 5 mmol), and piperidine **3a** (0.55 ml, 5.5 mmol) in methanol (10 ml) was stirred at 50°C till dissolution of reagents; then **4b** (1.0 g, 5 mmol) was added and the resulting mixture was stirred at room temperature for 1 h. Then acetic acid (0.5 ml) was added and after 30-min stirring the reaction mixture was poured into of (100 ml) water. The precipitate was separated and after recrystallization from ethanol nicotinamide **10** (0.40 g, 20%) as yellow crystals was obtained, mp 218-220°C. From the remaining filtrate after 5 days, N-methyl-2-(4-phenyl-1,3-thiazol-2-yl)acetamide (**11**) (0.14 g, 12%) as colorless crystals was separated by filtration, mp 100–102°C.

B. A mixture of compounds **1** (0.31 g, 2 mmol), **2b** (0.27 g, 2 mmol), and piperidine **3a** (0.3 ml, 3 mmol) in 5 ml of ethanol was stirred at 50°C till dissolution of reagents, then **4b** (1.0 g, 5 mmol) was added and the resulting mixture was refluxed for 1 h. Then acetic acid (0.3 ml) was added and after 30-min stirring the reaction mixture was poured into water (50 ml). The precipitate was separated and after recrystallization from ethanol nicotinamide **10 (**0.39 g, 48%) as yellow crystals was obtained, mp 218–220°C. From the remaining filtrate after 5 h, N-methyl-2-(4-phenyl-1,3-thiazol-2-yl)acetamide (**11**) (0.11 g, 24%) as colorless crystals was separated by filtration, mp 100-102°C.

Cyclocondensation of [11 + 1 + 3a]. A mixture of compounds **11** (0.70 g, 3 mmol), **1** (0.46 g, 3 mmol), and piperidine **3a** (0.3 ml, 3 mmol) in 10 ml of ethanol was stirred at room temperature for 1 h. Then acetic acid (0.35 ml) was added and after 30-min stirring the reaction mixture was poured into water (50 ml). The precipitate was separated and after recrystallization from ethanol **2-amino-1-methyl-6-oxo-4-phenyl-5-(4-phenyl-1,3-thiazol-2-yl)-1,6-dihydropyridine-3-carbonitrile** (**16**) (0.27 g, 23%) as yellow crystals was obtained, mp 258-259°C. IR spectrum, ν, cm^{-1}: 3430, 3320, 3225 (NH_2); 2215 (C≡N); 1652 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.53 (3H, s, NCH_3); 7.1-7.6 (10H, m, $2C_6H_5$); 7.78 (1H, s, thiazolyl H-5); 7.97 (2H, br. s, 6-NH_2). Found, %: C 68.49; H 4.12; N 14.29; S 8.36. $C_{22}H_{16}N_4OS$. Calculated, %: C 68.73; H 4.19; N 14.57; S 8.34.

Cyclocondensation of [11 + 1 + 3c]. A mixture of compounds **11** (1.16 g, 5 mmol) and **1** (0.77 g, 5 mmol) in methanol (10 ml) shortly heated till dissolution. Then 2N NaOMe **3c** (2.6 ml) was added, the reaction mixture was stirred for 1 h at the ambient temperature, acetic acid (0.5 ml) was added and the resulted reaction mixture poured into 100 ml of water. The precipitated crude product was dissolved in ethanol (15 ml) and during 5 days the precipitated crystals were separated by filtration to give compound **16** (0.61 g, 32%) as yellow crystals, mp 258-259°C.

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