New Materials, Compounds and Applications
Vol.4, No.1, 2020, pp.5-9

SYNTHESIS AND ANTIMICROBIAL PROPERTIES OF SOME THIAZOLE AND PYRIDINE DERIVATIVES

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Abstract. It was confirmed, that by condensation of thiosemicarbazide derivative of camphor with phenacyl bromide in ethanol and at the presence of piperidine, the corresponding thiazole derivatives are formed. By the interaction of camphor's thiosemicarbazide derivative with methyl ester of α-bromoacetic acid in the same reaction conditions, the corresponding thiazolidone derivative was synthesized. The way of synthesis of benzylamine the iminopyridine derivative by the one-pot three-component reaction of p-bromobenzylidene malononitrile with malononitrile has been developed. Synthesized pyridine derivative demonstrates high antimicrobial activity. Structures of all synthesized compounds confirmed by NMR spectroscopy.

Keywords: *thiosemicarbazone, phenacyl bromide, thiazole, iminopyridine, NMR.*

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Received: *05 December 2019;* ***Accepted:*** *25 February 2020;* ***Published:*** *30 April 2020.*

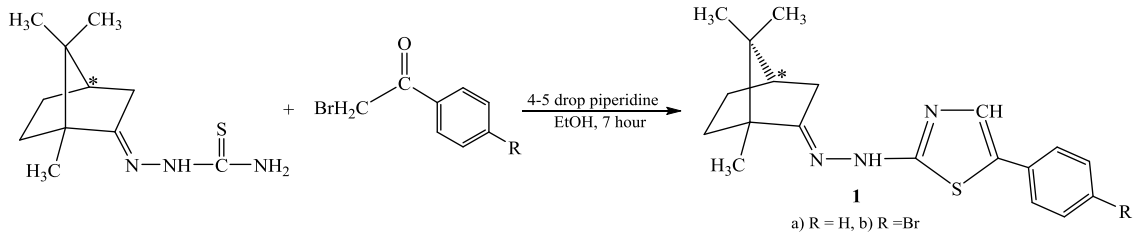
1. Introduction

The double-bonded compounds based on various methylenactive molecules have been synthesized (Naghiyev *et al.*, 2018). Various researchers investigated antimicrobial properties of synthesized new thiazole and thiophene derivatives (Khalil *et al.*, 2009; Liarasa *et al.*, 2011; Abdel-Galil *et al.*, 2018; Biernasiuk *et al.*, 2019). Pyridine derivatives have been synthesized by the interaction of 2-amino substituted benzothiazoles with 2-chlorpyridine-3-carboxyl acid and the antimicrobial properties of the reaction product were investigated (Patel *et al.*, 2011). Structures and antimicrobial properties of pyridine derivatives complexes have been studied (Kaushal *et al.*, 2018). Pyridone derivatives have been synthesized on the base of ylidensianoacetamides and ylidenemalononitriles that are an example of compounds with the polarized double bond (Naghiyev, 2019a, 2019b). Pyridine derivatives based on activated alkynes and amines have been obtained with the satisfied yield (Kiruthika *et al.*, 2011). Synthesis of appropriate pyridine derivatives was performed using benzalacetones and malononitrile dimer (Bardasov *et al.*, 2019). Imidazopyridines and iminopyridines were obtained by three-component reaction of benzylidinemallonitrile (Naghiyev *et al.*, 2018; Magerramov *et al.*, 2018). An effective method for the synthesis of new tricyclic pyrano[3,2-c]pyridines based on the condensation of benzylidenemononitrile was suggested (Mamedov *et al.*, 2019). The dependence of the biological activity of some chalcone derivatives on their molecular structure have been studied (Mamedov *et al.*, 2017). Molecular dynamics in the system solution of 6-methyl-2-phenyl-2,3-dihydro-

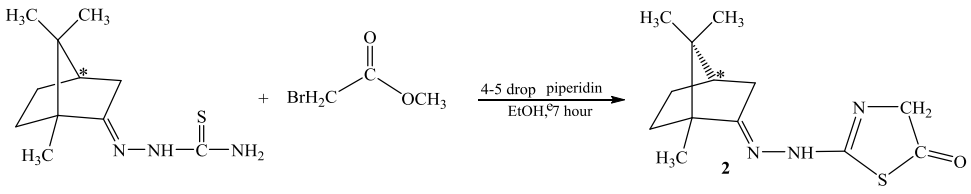
4H-chromene-4-on and 6-methyl-2-(4-nitrophenyl)-2,3-dihydro-4H-chromene-4-on (flavanone) were studied by using NMR spectroscopy (Mamedov *et al*., 2013).

2. Results and discussions

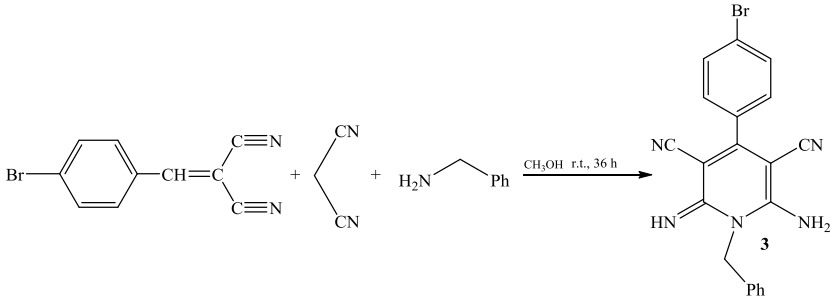
By the interaction of (R)-camphor thiosemicarbazone with phenacyl bromide and 4'-bromophenacyl bromide in the presence of catalytic amount of piperidine and in ethanol, the corresponding 5-phenyl-2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1] heptane-2-ylidene)hydrazi-nyl)thiazol (**1a**) and 5-(4-bromophenyl)-2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-yli-dene)hydrazinyl)thiazol (**1b**) have been formed.



2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptane-2-ylidene)hydrazinyl)thiazol-5(4H)-one (**2**) was obtained by the interaction of camphor thiosemicarbazone with methyl ester of α-bromoacetic acid in ethanol and the presence of the catalytic amount of piperidine.



As a result of one-pot, three-component catalyst-free reaction of pbromobenzylidenemalononitrile with malononitrile and benzylamine in the methanol, the corresponding iminopyridine derivative (**3**) have been obtained.



By antimicrobial screening of synthesized compounds was confirmed, that only compound (**3**) demonstrates good antimicrobial activity against *E.coli* and *B.subtilis* (zones of inhibition were 20 and 18 mm accordingly).

Compounds (**1a, b** and **2**) demonstrated low antimicrobial activities.

3. Experimental part. General remarks

All commercially available chemicals were obtained from Merck and Fluka (Sigma Aldrich) companies and used without further purification. Melting points were measured on Stuart SMP30 apparatus without correction. ^{1}H, ^{13}C NMR spectra were recorded on Bruker Avance 300-MHz spectrometer at 300 and 75 MHz, respectively. Thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel (60 F254) was used to monitor the progress of reactions.

Antibacterial activity

Growth inhibition of the substances 1-3 against two Gram-positive (*Bacillus subtilis, Staphylococcus aureus*) and two Gram-negative (*Escherichia coli, Pseudomonas aeruginosa*) bacterial strains (see below) was determined by the agar diffusion method at 37°C.

Experimental procedures:

5-Phenyl-2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene) hydrazineyl)thiazole (1a): 1 g (4.4 mmol) of (E)-2-((1S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine-1-carbothioamide and 0.89 g (4.5 mmol) of phenacyl bromide were dissolved in 40 ml of ethanol. A 4-5 drops of piperidine was added to the reaction mixture and reflux for 7 hours. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of the solvent, filtered, recrystallized from the ethanol-water mixture and obtained in pure form (yield 1.15 g, 79.86%). $T_{mp.}$ = 235°C.

^{1}H NMR spectrum (DMSO-d_6, δ, m.h.): 0.72 (s, 3H, CH_3); 0.90 (s, 3H, CH_3); 0.98 (s, 3H, CH_3); 1.21-1.33 (t-t, 2H, CH_2); 1.77 (k, 2H, CH_2); 2.02 (d-d, 2H, CH_2); 2.50 (m, 1H, CH); 4.59 (s, 1H, NH); 7.27 (s, 1H, CH=); 7.32 (t, 1H, CH_{arom}); 7.42 (t, 2H, $2CH_{arom}$); 7.81 (d, 2H, $2CH_{arom}$). ^{13}C NMR spectrum (DMSO-d_6, δ): 11.58, 18.94, 19.68, 27.25, 32.81, 35.41, 43.88, 48.18, 52.89, 104.06, 126.08, 128.58, 129.19, 133.19, 147.46, 168.18, 170.42.

5-(4-Bromophenyl)-2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinyl)thiazole (1b): Synthesized by the same way (yield 1.31 g, 73.18%). $T_{mp.}$ = 251°C.

^{1}H NMR spectrum (DMSO-d_6, δ, m.h.): 0.74 (s, 3H, CH_3); 0.91 (s, 3H, CH_3); 0.98 (s, 3H, CH_3); 1.25-1.39 (t-t, 2H, CH_2); 1.80 (k, 2H, CH_2); 2.03 (d-d, 2H, CH_2); 2.51 (m, 1H, CH); 5.49 (s, 1H, NH); 7.29 (s, 1H, CH=); 7.59 (d, 2H, $2CH_{arom}$); 7.78 (d, 2H, $2CH_{arom}$). ^{13}C NMR spectrum (DMSO-d_6, δ): 11.49, 18.99, 19.76, 27.36, 32.92, 35.52, 44.02, 48.33, 53.07, 104.79, 128.01, 130.10, 131.42, 132.00, 165.85, 169.10, 170.54.

2-(2-((1S,4R,E)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinyl)thiazol-5(4H)-one (2): 1 g (4.4 mmol) of (E)-2-((1S,4R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazine-1-carbothioamide and 0.75 g (0.0045 mol) of ethyl bromoacetate were dissolved in 40 ml of ethanol. A 4-5 drops of piperidine was added to the reaction mixture and reflux for 7 hours. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 3:1). Crystals were precipitated after evaporation of the solvent, filtered, recrystallized from the ethanol-water mixture and obtained in pure form (yield 0.93 g, 78.81%). $T_{mp.}$ = 208°C.

^{1}H NMR spectrum (DMSO-d$_6$, δ, m.h.): 0.68 (s, 3H, CH$_3$); 0.86 (s, 3H, CH$_3$); 0.91 (s, 3H, CH$_3$); 1.25 (m, 2H, CH$_2$); 1.75 (k, 2H, CH$_2$); 1.95 (d-d, 2H, CH$_2$); 2.41 (d, 1H, CH); 3.75 (s, 2H, CH$_2$CO); 8.48 (s, 1H, NH). ^{13}C NMR spectrum (DMSO-d$_6$, δ): 11.63, 18.93, 19.69, 27.22, 32.78, 33.13, 36.25, 43.70, 47.86, 52.70, 162.59, 174.50, 177.88.

6-Amino-1-benzyl-4-(4-bromophenyl)-2-imino-1,2-dihydropyridine-3,5-dicarbonitrile

(3): Mixture of p-bromobenzylidenemalononitril (5.1 mmol) and malononitrile (5.2 mmol) was dissolved in 35 ml of methyl alcohol and stirred for 5-7 minutes. Benzylamine (5.2 mmol) was added to mixture in vigorous stirring condition. The progress of the reaction was monitored by TLC (EtOAc/n-hexane, 2:1). The reaction mixture stayed for 48-72 hours. When the solvent evaporates, then crystals sedimented. Crystals filtered by filter paper and recrystallized from mixture the ethanol-water. Yield 60.60%. T$_{mp}$=225°C.

^{1}H NMR spectrum (300 MHz, DMSO-*d6*) δ ppm; 4.59 (d, 2H, CH$_2$N, $^{3}J_{H\text{-}H}$=5.7); 7.21-7.77 (m, 11H, 9ArH+NH$_2$); 8.14 (t, 1H, NH=, $^{3}J_{H\text{-}H}$=5.7). ^{13}C NMR spectrum (75 MHz, DMSO-*d6*) δ 44.21 (CH$_2$N), 79.53 (=C$_{quat.}$), 80.66 (=C$_{quat.}$), 116.83 (CN), 116.83 (CN), 123.98 (C$_{arom}$), 127.25 (3CH$_{arom}$), 128.33 (2CH$_{arom}$), 130.97 (2CH$_{arom}$), 132.11 (2CH$_{arom}$), 134.79 (C$_{arom}$), 139.91 (C$_{arom}$), 158.97 (=C$_{quat.}$), 159.25 (=C$_{quat.}$), 161.27 (=C$_{quat.}$).

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