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REGIOSELECTIVE BROMINATION OF 2-IODOMETHYL-2,3-DIHYDROTHIAZOLO[3,2-*a*]PYRIMIDIN-5-ONE

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Abstract – The bromination reactions of 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one were carried out using bromine and NBS as the brominating agent. Depending on the brominating agent used and a solvent two bromo derivatives were obtained: the product of electrophilic substitution in the pyrimidine ring and the product containing two bromine atoms which was formed as a result of two parallel reactions – an electrophilic substitution on the pyrimidin ring and a nucleophilic substitution of iodine. The position of bromine atoms in the obtained compounds was confirmed using ^{1}H NMR spectrum.

The compounds containing fused thiazole and pyrimidin rings play a significant role in organisms due to their biological activity. Some of them, ritanserin and setoperone (Figure 1), are known as antagonists of $5HT_2$ serotonine receptors. Moreover, ritanserin also binds receptors to dopamine D_2 and it is effective as

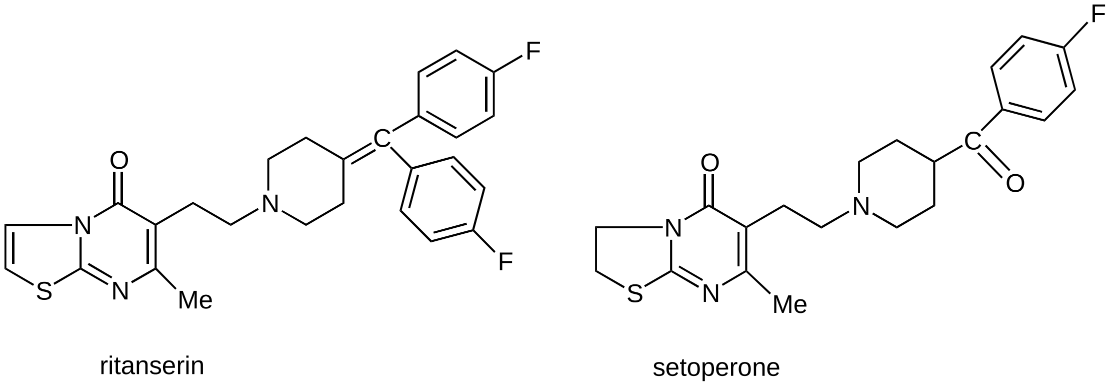
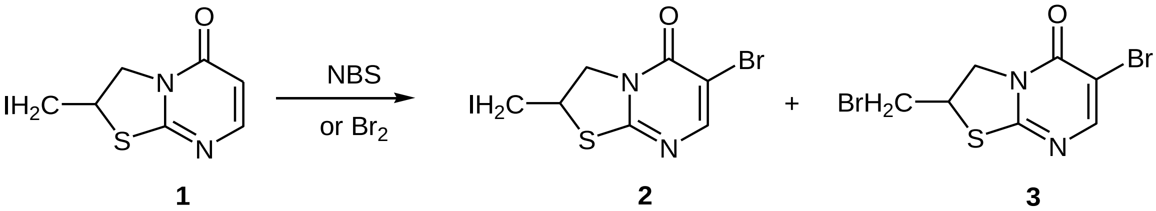


Figure 1. Ritanserin and setoperone as examples of biologically active thiazolopyrimidine derivatives

a treatment of patients with chronic schizophrenia.[1,2] Other thiazolo[3,2-*a*]pyrimidin-5-one derivatives display antibacterial, antituberculosis,[3] anti-viral[4] or anti-inflammatory[5] actions.

In our previous work we focused on the synthesis of thiazolopyrimidine systems *via* the reaction of closing the thiazole ring. We also modified 7-methylthiazolo[3,2-*a*]pyrimidine derivative *via* electrophilic substitution reactions.[6-8] Currently, the bromination reaction of 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**1**) using NBS (*N*-bromosuccinimide) and bromine, in various solvents was conducted. The bromination reaction of this compound led to two products: 6-bromo-2-(iodomethyl)-2,3-dihydrothiazolo-[3,2-*a*]pyrimidin-5-one (**2**) and 6-bromo-2-(bromomethyl)-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**3**) (Scheme 1).



Scheme 1. Bromination of 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**1**)

Bromination of aromatic systems was carried out using NBS or Br_2 as a brominating agent. A bromination reaction with bromine was initially performed in DMF.[9] Low degree of conversion of **1** towards **3** and high selectivity (more than 97%) were observed (Table 1). Product **3** was formed as a result of two parallel reactions: electrophilic substitution in the pyrimidine ring and nucleophilic substitution of iodine atom in iodomethyl group. Due to the low conversion, the reaction was carried out in other solvents such as THF and MeCN, which were previously described for the bromination using NBS.[10-13] In the case of using bromine as a brominating agent the highest conversion (92.6%) was obtained in MeCN.

Table 1. The ratio of bromination products of **1** depending on the brominating agent and solvent

Brominating reagent	Solvent	Time [h]	Conversion[a] [%]	Ratio of product[a] [%]	
				2	**3**
Br_2	DMF	1	55.4	2.7	97.3[c]
	MeCN	1	92.6	4.0	96.0
	THF	1.5	51.5	17.9	82.1
	[BMIM]PF_6	1	100.0	3.9	96.1
	[BMIM]Br[b]	1	100.0	0.0	100.0[d]

NBS	MeCN	2.5	97.6	92.2[e]	7.8
	THF	5	77.5	86.8	13.2
	[BMIM]PF$_6$	1	70.3	57.3	41.7
	[BMIM]Br[b]	1	85.1	1.9	98.1

[a]Conversion and ratio of product was determined by HPLC (the retention times in MeOH:water 60:40 were respectively: 5.59 min. for 1, 8.36 min. for 2 and 7.34 min. for 3), [b]70 ºC, [c]Isolated yield – 37%, [d]Isolated yield – 91%, [e]Isolated yield – 63%

The results of bromination reaction with bromine prompted us to use a milder brominating agent in order to verify the possibility of obtaining product **2** containing one bromine atom on the pyrimidine ring. We conducted the bromination reaction of 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one **1** using NBS in THF and MeCN at room temperature. The degree of conversion of **1** was 97.6% in MeCN and 77.5% in THF and the product **2** was obtained in high chemoselectivity - 92.2% and 86.8% respectively. The high polarity of a solvent facilitated the ionization of the NBS molecules.

The dependence of the reaction yield on the solvent polarity in the case of using both bromine and NBS as a brominating agent prompted us to carry out the bromination reactions with the use of ionic liquids as a reaction medium. Previous reports have shown that the use of ionic liquids in the bromination of aromatic systems with NBS leads to the bromination product in high yield and high selectivity.[14-16]

Similarly to organic solvents, in ionic liquid the composition of the reaction mixture depended on the brominating agent used. Regardless of the solvent, in the bromination reaction with Br_2 the main reaction product was the compound **3** which was a result of the course of the two substitution reactions: electrophilic and nucleophilic. In the ionic liquid [BMIM]Br, the reaction occured completely selectively. The compound **3** was the only product of the bromination. The use of the ionic liquid as a reaction medium increased the rate of reaction in comparison with organic solvents. Therefore, after 1 hour the conversion in ionic liquids was 100%. Exceptional polarity of ionic liquids enables the polarization of binding Br_2 and consequently increases the reactivity of the reagent.

Compound **3** was predominantly formed also in [BMIM]Br using NBS as a brominating agent. The selectivity of the transformation was determined by the presence of NBS and the bromide ion forming a part of the ionic liquid and acting as the nucleophile. Beside the electrophilic substitution reaction of Br^+ ion in the pyrimidine ring, iodine was substituted by Br^- in the nucleophilic substitution. In [BMIM]PF$_6$ the degree of conversion of **1** into **3**, compared to conventional organic solvents, was also high. The compound **3** was detected as a 41.7% of the reaction mixture.

However, in this case, compound **2** was the main product of the bromination reaction which was obtained as a result of electrophilic aromatic substitution. A high yield of product **3** in [BMIM]PF$_6$ was probably caused by the increase in polarity of the reaction medium in comparison with organic solvents (logP = -2,39 for

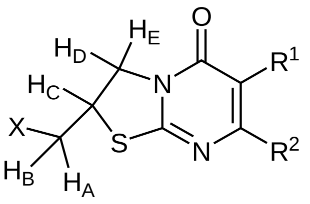
[BMIM]PF_6),[17] which may promote the reaction of nucleophilic substitution in –CH_2I group. For this reason beside the electrophilic substitution product **2**, the product **3** was obtained. This is in accordance with the literature reports showing that NBS generally used as a brominating agent acts as a donor Br^+ in the aromatic electrophilic substitution.[14-16] However, there are known reactions in which the nucleophilic substitution involving NBS may occur. The bromination reaction of alcohols or thiols in the presence of triphenylphosphine is the example of it.[18,19]

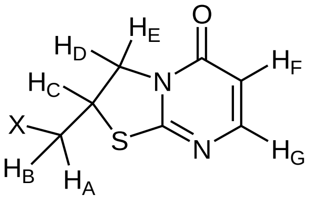
Identification of the bromination reaction products by ^1H NMR

In order to determine the position of bromine atoms in the molecules **2** and **3**, ^1H NMR spectra of the products **1** and **2** were compared with the spectra of suitable 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one derivatives obtained previously (compounds **4** – **7**)[6,7] (Table 2). ^1H NMR spectra analysis revealed that in the case of products **2** and **3** the proton signals at $\delta = 7.97 - 8.04$ ppm were observed. These values are comparable to the signal of the proton H_G observed for compounds **4** and **7**, while no signal of H_F proton was observed. In the previously prepared compounds **4** - **6** it was observed at $\delta = 6.03 - 6.20$ ppm. This confirms that the bromination using both NBS and bromine occured at C-6 of the thiazolo[3,2-*a*]pyrimidin-5-one. The presence of the bromine atom in the 2-bromomethyl group of compound **3** caused a shift of protons H_A and H_B signals towards of higher values δ in comparison with 2-iodomethyl group. In the case of the compound **6** containing 2-bromomethyl group analogous shift was observed.

The presence of one bromine atom in the molecule of compounds **2** and two bromine atoms in the molecule of compound **3** also was confirmed *via* characteristic signals system in the mass spectrum descended from the two isotopes of bromine ^{79}Br and ^{81}Br.

Table 2. The comparison of chemical shifts in the ^1H NMR spectra of the 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one derivatives **2** - **7**





No.	R^1	R^2	X	H_A	H_B	H_C	H_D	H_E	H_F	H_G
2	Br	H	I	3.42	3.54	4.18	4.45	4.63	-	8.04
3	Br	H	Br	3.50	3.60	4.11	4.38	4.67	-	7.97

4	H	H	I	3.40	3.52	4.13	4.39	4.58	6.20	7.74
5	H	Me	I	3.38	3.53	4.11	4.36	4.55	6.03	-
6	H	Me	Br	3.53	3.64	4.10	4.34	4.67	6.03	-
7	Me	H	I	3.40	3.53	4.16	4.41	4.61	-	7.63

In conclusion we obtained two bromo-derivatives of 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one. In the bromination reaction with bromine, regardless of solvent used the dibromo-derivative was the main product of the reaction. It was caused by two reactions running parallel: an electrophilic substitution in the pyrimidin ring and-a nucleophilic substitution of iodine atom. When NBS was used in organic solvents monobromo-derivative was predominantly obtained by electrophilic substitution reaction in the pyrimidine ring. The use of ionic liquids as reaction medium significantly increased the participation of dibromo-derivative.

EXPERIMENTAL

General information

^{1}H NMR and ^{13}C NMR spectra were recorded on the Bruker 400 MHz apparatus (TMS as an internal standard). MS spectra were recorded on the Finnigan MAT 95. UV spectra were recorded on the spectrofotometer Aquarius 7250 Cecil Instruments. The HPLC experiments were performed on the Shimadzu HPLC system (Japan) equipped with solvent delivery pump LC-20AD, UV–VIS detector model SPD-20A, degasser model DGU-20A5, an column oven model CTO-20A and a column LiChrospher(TM) 100 RP-18 (5μm), Merck (Germany). The solvents: methanol and water for HPLC from POCH (Poland) were used.

2-Iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**1**) was synthesized according to Studzińska et al.[6] All other chemicals and solvents were purchased commercially and used without further purification, unless otherwise noted.

Preparative scale bromination of 1

*Synthesis of 6-bromo-2-(iodomethyl)-2,3-dihydrothiazolo[3,2-a]pyrimidin-5-one (**2**)*

1 mmol (0.294 g) of 2-Iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**1**) was dissolved in 6 mL MeCN and 1.1 mmol (0.196 g) *N*-bromosuccinimide (NBS) was added. The mixture was stirred for 2.5 h at room temperature and then concentrated. The crude product was purified by PLC (Preparative layer plates) using hexane:EtOAc 6:4 as eluent. Isolated yield of **2** – 63%, mp 104-105 °C, UV (H_2O + 5% EtOH): λ_{max} [nm] ($\varepsilon_{max}\cdot 10^3$) = 200.5 (14.63), 245 (7.48), 306.5 (10.03), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.42 (dd, *J* = 4.0 8.0 Hz, 1H, C$\underline{H_A}$I), 3.54 (dd, *J* = 2.0 8.0 Hz, 1H, C$\underline{H_B}$I), 4.18 (m, 1H, C^2-$\underline{H}$), 4.45 (dd, *J* = 8.0 12.0 Hz,

1H, C^3-<u>H</u>$_C$), 4.63 (dd, J = 4.0 12.0 Hz, 1H, C^3-$\underline{H_D}$), 8.04 (s, 1H, C^7-$\underline{H}$), ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 157.2, 154.0, 109.1, 54.7, 44.3, 6.2, MS EI: *m/z* = 372.0 (11.0%, $M^{+\cdot}$), 374.0 (10.6%, $M^{+\cdot}$ + 2), 245.1 (100.0%, $M^{+\cdot}$ - 127), 247.1 (98.2%, $M^{+\cdot}$ + 2), HRMS Found: 371.8443, HRMS Calc. for $C_7H_6N_2OS^{79}BrI$: 371.8429

*Synthesis of 6-bromo-2-(bromomethyl)-2,3-dihydrothiazolo[3,2-a] pyrimidin -5-one (**3**)*

Procedure 1: 1 mmol (0.294 g) 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**1**) was dissolved in 6 mL DMF and 1 mmol (51 μL) bromine was added. The mixture was stirred for 1 h at room temperature and then concentrated. The crude product was purified by PLC using hexane:EtOAc 2:5 as eluent. Isolated yield of **3** – 37%,

Procedure 2: 1 mmol (0.294g) 2-iodomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-5-one (**1**) was dissolved in 6 mL [BMIM]Br (melted in 70 °C) and 1 mmol (51 μL) bromine was added. The mixture was stirred for 1 h at 70 °C. After cooling the water (5 mL) was added. The product was isolated by the extraction with EtOAc. Isolated yield of **3** – 91%, mp 200-205 °C, UV (H_2O + 5% EtOH): λ_{max} [nm] ($\varepsilon_{max} \cdot 10^3$) = 203 (10.60), 244.5 (5.76), 305.5 (8.35), ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 3.50 (dd, J = 4.0 8.0 Hz, 1H, $C\underline{H_A}Br$), 3.60 (dd, J = 2.0 8.0 Hz, 1H, $C\underline{H_B}Br$), 4.11 (m, 1H, C^2-$\underline{H}$), 4.38 (dd, J = 8.0 12.0 Hz, 1H, C^3-$\underline{H_C}$), 4.67 (dd, J = 2.0 12.0 Hz, 1H, C^3-$\underline{H_D}$), 7.97 (s, 1H, C^7-$\underline{H}$), ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7, 152.1, 148.8, 103.9, 48.0, 38.7, 27.7, MS EI: *m/z* = 323.9 (53.6%, $M^{+\cdot}$), 325,9 (100%, $M^{+\cdot}$ + 2), 328.0 (54.9%, $M^{+\cdot}$ + 4), HRMS Found: 323.85678, HRMS Calc. for $C_7H_6N_2OS^{79}Br_2$: 323.8566

Analytical scale bromination of 1

In a typical experiment, a reaction was performed in a solution containing substrate **1** (17 μmol, 5 mg), brominating agent (18.7 μmol, 3.3 mg NBS and 17 μmol Br_2 respectively), solvent (100 μL). In the case of bromine used, 20 μL of bromine was dissolved in 0.980 mL of a corresponding solvent. 44 μL of the solution and 56 μL of the solvent were added to the substrate **1**. The mixture was stirred at room temperature (in the case of [BMIM]Br the temperature of reaction was 70 ºC). The reaction progress was monitored by TLC and HPLC. After the reaction a sample of 20 μL was taken from a reaction mixture and then it was concentrated. 2 mL of MeOH was added. The ratio in the mixture of **1**, **2** and **3** compounds was determined on an HPLC system using a RP-18 column. Sample injection volume was 0.01 mL. The mobile phase consisted of methanol:water (60:40). The retention times were respectively: 5.59 min. for **1**, 8.36 min. for **2** and 7.34 min. for **3**.

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