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REACTION OF 6-AMINO-2-METHYLBENZOPYRIMIDIN-4-ONE WITH ARYL SULFACHLORIDES

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Abstract

As a result of studying the synthesis and biological activity of condensed heterocyclic compounds, new drugs have been developed, including derivatives of 6-aminobenzopyrimidin-4-one, and their bioactive derivatives have been identified. The development of new drugs based on them is relevant.

Keywords: *o-aminobenzoic acid, thyoacetamide, cyclization, nitration, reducation, 2-alkhylbenzopyrimidin-4-one, 6-amino-2-alkhylbenzopyrimidin-4-one, IR, ^{1}H and ^{13}C NMR*

Introduction

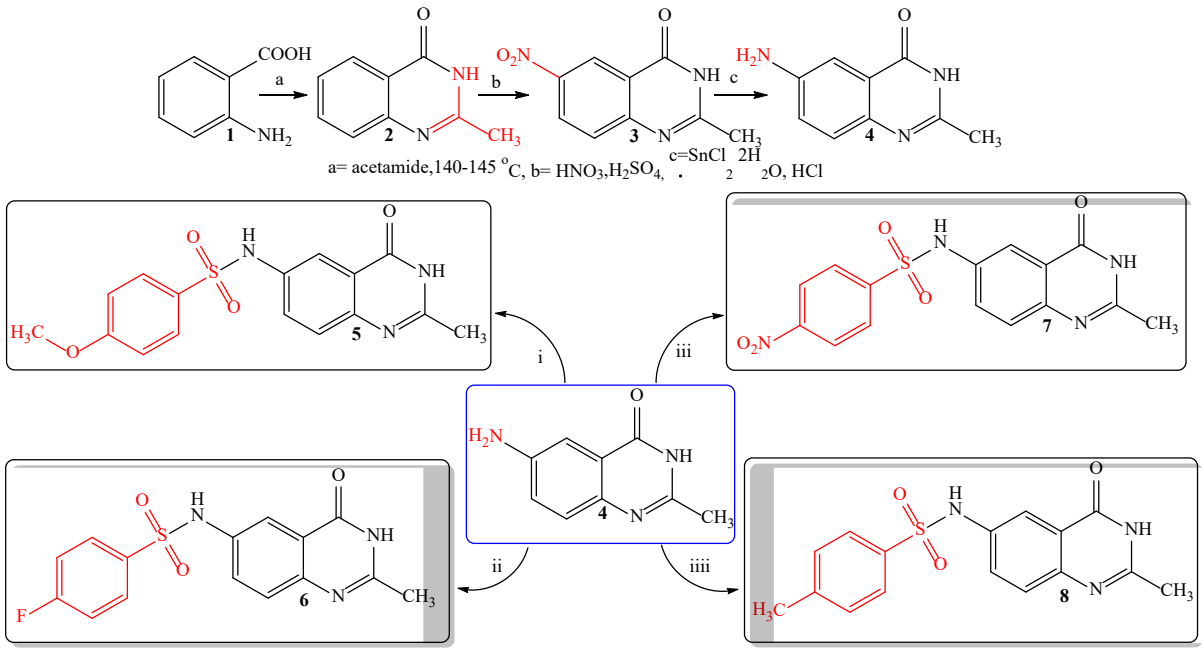
In recent years, most representatives of drugs created in various fields of agriculture and modern medicine are derivatives of compounds containing a condensed pyrimidine ring. In recent years, as a result of the study of synthesis and biological activity of condensed heterocyclic compounds, new drugs have been developed (Pawan K. Pawan K., Premnath D., Muhammad T., Mazlee S., Yaman M., Nurul S., Muhammad S. et al., 2019). Among them we can point out the majority of quinazoline derivatives in the second and third states of the condensed pyrimidine ring. Compounds based on benzopyrimidin are widely used against viruses, microbes, fungi, colds and cancer (Xiaoqing Wu, Mingdong Li, Yang Qu, Wenhua Tang, Youguang Zheng, Jiqin Lian, Min Ji, Liang Xu., 2010), and as stimulants for plants (Raffaella Sordella, Daphne W. Bell, Daniel A. Haber, Jeffrey Settleman. 2004). Anticancer drugs prepared from compounds of the benzopyrimidin family have shown a very low level of toxicity (Muhammad T., Mazlee S., Yaman M., Nurul S., Muhammad S. et al., 2019). In this

regard, especially the N-6 state electrophilic substitution reactions (Zulpanov F. A., Elmuradov B.J, Saitkulov F. E., Arzanov R. X., 2024), i.e. synthesis of new types of derivatives with various halogen compounds of alkyl halides, and with the change of their functional group, it is possible to find new types of fundamental systematic laws and among them, bioactive compounds. Avast number-of quinazoline derivatives have been synthesized to provide synthetic drugs and to design more effective medicines. There are a number of reviews and monographs on quinazoline and quinazoline alkaloids. Recently, we have documented a formal collection of significant developments (2013) on the synthetic methods through which these heterocycles (quinazolines and quinazolinones) could be accessed, along with diverse biological profile which they possess. Some other groups also published independently the synthesis of quinazolinones and bioactive quinazolines, respectively. There has been no dicussion on the mechanistic aspects of key transformations. So, incorollary of these fascinating findings as well as part of a programme aimed at discovering heterocyclic structures with various pharmacological properties, in general, and in continuation of our previous work on these skeletons, we report here the very recent developments (2014) in the environmentally benign, green, and efficient synthetic protocols (in most cases) to access quinazoline and quinazolinone derivatives from cheap and readily available commercial feedstocks. Quinazolinone and their derivatives are also building block for approximately 150 naturally occurring alkaloids isolated from a numberoffamilies of theplant kingdom, frommicroorganisms and animals. Some of the compounds incorporating quinazolinone motif like raltitrexed and thymitaq possess antitumor activities (Zulpanov F. A., Elmuradov B.J, Saitkulov F. E., Arzanov R. X. 2024; Sordella R., Bell D. W., Haber D. A. and Settleman J. 2004; Deng X. Q., Zheng Y., Yuan Y. P., Quan Z. S., Guan L. P.; 2012; Petrov K. G., Zhang Y. M., Carter M., Cockerill G. S., Dickerson S., Gauthier C. A., Guo Y., Mook R. A. Jr, Rusnak D. W., Walker A. L., Wood E. R., Lackey K. E., 2006; Imtiaz Khana, Aliya Ibrar, Waqas Ahmed, Aamer Saeed. 2014). The refore bicyclic benzopyrimidin-4-ones are of great practical and theoretical interest.

Methods and results

Results and discussion

An efficient and convenient method for the synthesis of 2- methylbenzopyrimidine-4-one in high yields was developed by the reaction of o-aminobenzoic acid with thioacetamide.



i=4-Methoxybenzenesulfonyl chloride,ii=4-Fluorobenzenesulfonyl chloride,iii=4-Nitrobenzenesulfonyl chloride,iiii4-Toluenesulfonyl chloride,

Under the influence of a nitrating mixture of the synthesized substance, 2-methyl-6-nitrobenzopyrimidine-4-one was synthesized in a nitrolab with a yield of 95%. The resulting nitroblock was reduced with tin (II) chloride dihydrate ($SnCl_2 \cdot 2H_2O$) and HCl to obtain the corresponding 6-amino-2- methylbenzopyrimidine-4-one (1) with a yield of 65%. Then, 6-amino-2-methyl quinazolin-4-one (1) was synthesized in the presence of aryl sulfochlorides in the presence of DMF solvent and K_2CO_3. The structure of the obtained substances was studied using physical research methods: IR, 1H and 13C NMR spectra, and their in-depth analysis fully proved that they correspond to the proposed structure.

Experimental part

Synthesis of 2-methylbenzopyrimidin-4-one (1). 1.37 g (0.01 mole) of o-aminobenzoic acid and 1.52 g (0.02 mole) of thioacetamide were added to a 100-ml round bottom flask and heated for 2-3 hours in an oil bath connected with a reflux condenser at 140-145°C, first it boils and then a solid is formed. The obtained solid is thoroughly rubbed in a mortar, 40 ml of 5% aqueous NaOH solution is added, completely dissolved and brought to neutral (pH-7) medium by a weak solution of HCl. The precipitate is filtered and washed with distilled water. The substance is recrystallized from ethyl alcohol (C_2H_5OH) and as a yield 1.56 g (98%) of substance (**1**), melting point 238–140 °C, R_f = 0.73 (system: chloroform:methanol - 10:1) is obtained. IR spectrum (ν, cm^{-1}): :3171 cm^{-1} (C-N), 2979 cm^{-1} (C-H), 2990 cm^{-1} (C-H_2), 1669 cm^{-1} (C=O), 1609 cm^{-1} (C=N). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, ppm, δ, J/Hz): 8.06 (1H, ddd, J=7.9, 1.6, 0.6, H-5), 7.65 (1H, m, H-7), 7.49 (1H, m, H-8), 7.34 (1H, m, H-6), 5.72 (1H, broad s, NH), 2.36 (3H, s, H-9). ^{13}C NMR spectrum (100 MHz, DMSO-d6+CCl_4, ppm, δ): 154.24 (C-2), 162.24 (C-4), 120.74 (C-4a), 126.24 (C-5), 124.80 (C-6), 133.10 (C-7), 125.52 (C-8), 149.12 (C-8a), 21.45 (C-9).

Synthesis of 4-methoxy-N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl)benzenesulfonamide (4). Heteroaromatic compounds (4) (1.752 g, 0.01 mole) were dissolved in anhydrous acetone (5 ml) with dry pyridine (1.5 ml) and 4-methoxybenzenesulfonyl chloride (2.273 g, 0.011 mole) was added at room temperature. The reaction was heated to 50 °C for 24 hours. 4-methoxy-N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl)benzenesulfonamide **(4)** precipitated as a crystalline solid after suction filtration. The crude product was recrystallized from dimethylformamide (DMFA). The substance was synthesized with a high yield of 86%. R_f = 0.73.

Synthesis of 4-fluoro-N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl)benzenesulfonamide). Heteroaromatic compounds (4) (1.752 g, 0.01 mole) were dissolved in anhydrous acetone (5 ml) with dry pyridine (1.5 ml) and 4-methoxybenzenesulfonyl chloride (2.273 g, 0.011 mole) was added at room temperature. The reaction was heated to 50 °C for 24 hours. 4-methoxy -N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl)benzenesulfonamide **(4)** precipitated as a crystalline solid after suction filtration. The crude product was recrystallized from dimethylformamide (DMFA). The substance was synthesized with a high yield of 86%. R_f = 0.73.

Synthesis of N-(2-methyl-4-oxo-3, 4-dihydrobenzopyrimidine-6-yl)-4-nitrobenzenesulfonamide). Heteroaromatic compounds (4) (1.752 g, 0.01 mole) were dissolved in anhydrous acetone (5 ml) with dry pyridine (1.5 ml) and 4-methoxybenzenesulfonyl chloride (2.273 g, 0.011 mole) was added at room temperature. The reaction was heated to 50 °C for 24 hours. 4-methoxy-N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl)benzenesulfonamide **(4)** precipitated as a crystalline solid after suction filtration. The crude product was recrystallized from dimethylformamide (DMFA). The substance was synthesized with a high yield of 86%. R_f = = 0.73.

Synthesis of 4-methyl-N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl)benzenesulfonamide). Heteroaromatic compounds (4) (1.752 g, 0.01 mole) were dissolved in anhydrous acetone (5 ml) with dry pyridine (1.5 ml) and 4-methoxybenzenesulfonyl chloride (2.273 g, 0.011 mole) was added at room temperature. The reaction was heated to 50 °C for 24 hours.

4-methoxy-N-(2-methyl-4-oxo-3,4-dihydrobenzopyrimidine-6-yl) benzenesulfonamide **(4)** precipitated as a crystalline solid after suction filtration. The crude product was recrystallized from dimethylformamide (DMFA). The substance was synthesized with a high yield of 86%. $R_f = 0.73$.

Conclusion

An improved method for the quantitative synthesis of benzopyrimidin-4-one by heterocyclization in the presence of thioacetamide and o-aminobenzoic acid was developed. As a result of nitration reactions in the presence of a nitrating agent, the resulting substance was synthesized as 2-methyl-6-nitrobenzopyrimidin-4-ones. The reduction reaction was carried out in the presence of nitrobramic tin chloride digidate. The obtained substances were synthesized as important synthons for further modifications of sulfonamides in the presence of aryl sulfochloridates. The structure of the obtained substances was analyzed and confirmed using modern physical research methods

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