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SYNTHESIS OF UREA DERIVATIVES BASED ON SUBSTITUTED2-AMINOTHIAZOLES AND SOME AROMATIC ISOCYANATES

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Abstract

Synthesis of 1,3-substituted urea derivatives based on m-toluyl isocyanate and 2-aminothiazoles with different functional groups. Analysis of the structure of the obtained substances in modern physical research methods. 1,3-substituted urea derivatives were synthesized based on m-toluyl isocyanate and 2-aminothiazoles. The structure of the synthesized substances was proved by IR, ^{1}H NMR, ^{13}C NMR, spectral analysis.

Keywords: *m-Toluyl isocyanate, DMFA, K_2CO_3, 2-(3-(m-tolyl)urea)-4,5-dihydrothiazole-4-carboxylic acid, 1-(benzo[d]thiazol-2-yl)-3-(m-tolyl)urea*

Introduction

Modern search in the currently intensively developing chemistry and properties of urea compounds attract the attention of many researchers both in Uzbekistan and abroad (Suresh, G., Nadh, R.V., Srinivasu, N., Yennity, D., 2018; Das, D., Sikdar, P., Bairagi, M., 2016; Alexandru, M.-G., Velickovic, T.C., Jitaru, I., Grguric-Sipka, S., Draghici, C., 2010). This is due, on the one hand, to those rich capabilities of diphenyl, azo-diphenyl, bis-urea, polyhydrocarbon groups in molecules of organic macrocompounds, and on the other hand, with valuable practical using the properties of organic substances themselves compounds diphenyl, azodiphenyl groups, as well as bis-urea bonds. There are many examples where the introduction of azo-, phenyl, diphenyl bridging bonds would lead to the emergence of various kinds of biological, pharmacological, physiological activity, as well as the ability to inhibit corrosion of metals, coatings, and stabilizers for halogen-containing polymers, impregnations, and also as an anti-aging vulcanization of rubbers, the creation of solvation theories for intensifying the processes of dyeing and printing fabrics from natural and chemical fibers in liquid ammonia and organic solvents.

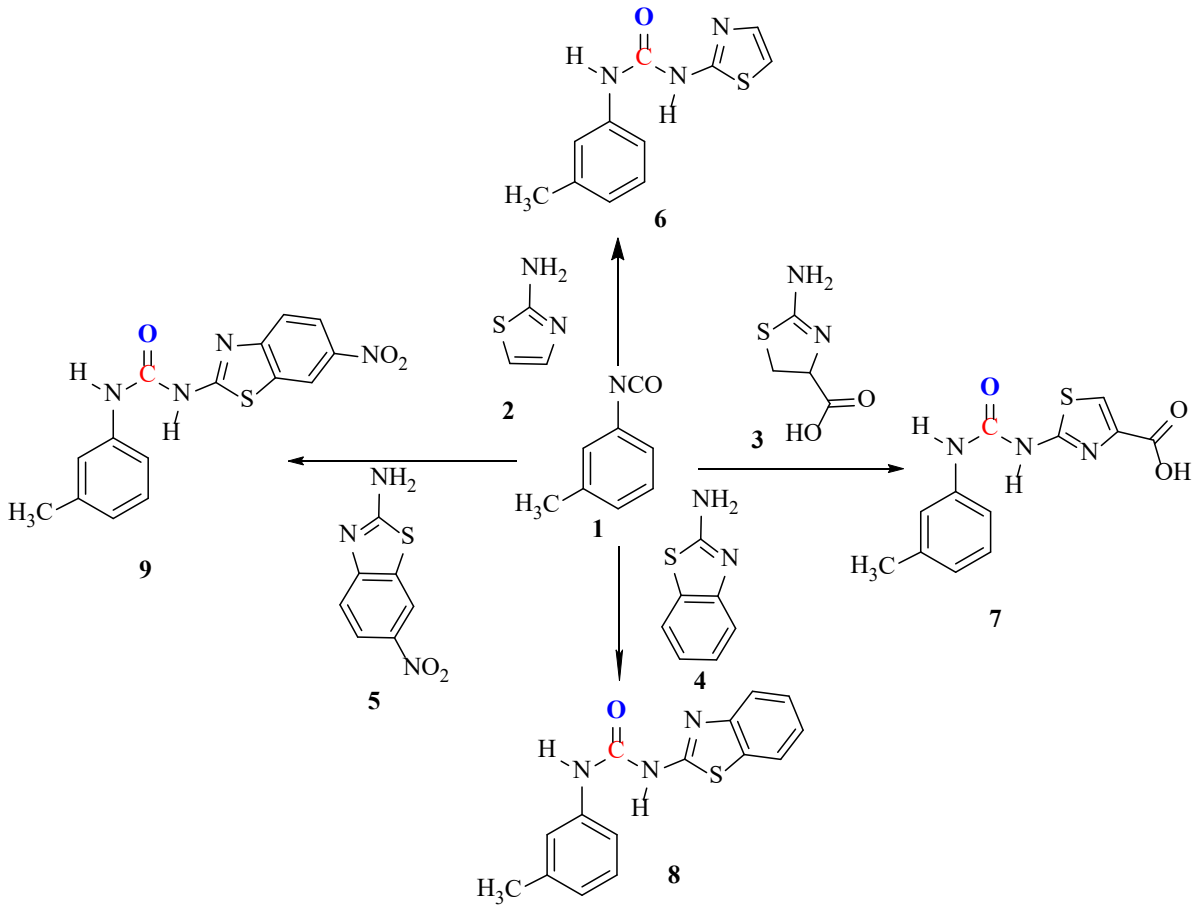
At present, the synthesis of urea derivatives kept by various pharmacophoric groups and the study of their biological activities are important tasks. Because among the compounds of this class there are many drugs against diabetes, cancer, hepatitis and

many other diseases, as well as substances with high fungicidal and herbicidal activity in agro-industry. That is why the synthesis of 1,3-substituted ureas, determination of their structure by physico-chemical methods and study of their biological activity are considered urgent issues.

Method and Results

Interest in the chemistry of 2-aminothiazole in recent years is explained by the discovery of a wide spectrum of biological activity in a number of its derivatives. In addition, the 2-aminothiazole molecule, which has a large number of reaction centers, cannot but interest chemists (Décor, A., Grand-Maître, C., Hucke, O., O'Meara, J., Kuhn, C., Constantineau-Forget, L., Brochu, C., Malenfant, E., Bertrand-Laperle, M., Bordeleau, J. 2013; Jalani, H. B., Pandya, A. N., Pandya, D. H., Sharma, J. A., Sudarsanam, V., Vasu, K. K., 2013; Stefanska, J., Nowicka, G., Struga, M., Szulczyk, D., Koziol, A. E., Augustynowicz-Kopec, E., Napiorkowska, A., Bielenica, A., Filipowski, W., Filipowska, A., 2015; Elshaarawy, R. F., Mustafa, F. H., Sofy, A. R., Hmed, A. A., Janiak, C., 2019; Chen, Y.-Y., Gopala, L., Bheemanaboina, R. R. Y., Liu, H.-B., Cheng, Y., Geng, R.-X., Zhou, C.-H., 2017; Prakash, A., Malhotra, R. 2018; Cordeiro, Y., Ferreira, N. C., 2015). Therefore, the goal of our work was to obtain new heterocyclic compounds based on 2-aminothiazole using the halocyclization reactionBased on the following reactions, 1,3-substituted urea derivatives were synthesized based on m-toluyl isocyanate and 2-aminothiazoles with different functional groups. As a result of the action of molecules of substances 2, 3, 4, 5 of raw material 1, corresponding products 6, 7, 8, 9 were synthesized in high yield.

Figure 1.



m-Toluyl isocyanate and 2-aminothiazoles 1,3-substituted urea derivatives were synthesized. Potash was used as a catalyst in the reaction. Factors affecting the course of the reaction were determined.

1,3-substituted aryl-heteryl urea derivatives were synthesized in good yields. -IK, 1H-NMR, 13S-NMR spectra of the obtained substances were analyzed.

Experimental Part

1-(THIAZOL-2-YL)-3-(M-TOLYL) UREA. 0.71 ml (5.48 mmol, 0.73 g, ρ = =1.033 g/ml) of m-toluyl isocyanate (1), 0.55 g (5.49 mmol) of 2-aminothiazole (2) were taken in a 100 ml round-bottom flask. 10 mL of DMFA was added to the flask and mixed on a magnetic stirrer. After the substances were completely dissolved, 0.83 g (6 mmol) of potash was added and mixed. The flask was stirred on a magnetic stirrer connected to a reflux condenser for 4–8 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was left at room temperature overnight. The precipitate was filtered off, extracted with K2SO3 and dried to give 1.08 g. (84%) product (6) was obtained. Rf =0.62 (benzene: methanol – 5:1). 1N YaMR (m.u CD3OD): 10.03 (1H, c, NH-), 7.70 (1H, c, Ar-H-2), 7.62 (1H, d, J=5,72, Ar-H-6), 7.48 (1H, d, J=3.64, Het H-4), 7.20 (1H, t, J=7.80, H_{Ar}-5), 6.98 (1H, d, J=3,64, H_{Het}-5), 6.83 (1H, d, J=7.54, H_{Ar}-4), 2.15 (3H, c, Alk-CH_3). **^{13}C NMR (CD_3OD):** 162.7 (C_{Het}-2), 153.9 (C=O C), 140.5 (Ar-C-3), 139.6 (C_{Ar}-1), 138.3 (C_{Het}-4), 129.8 (C_{Ar}-5), 124.7 (C_{Ar}-4), 121.0 (C_{Ar}-4), 117.0 (C_{Ar}-6), 112.7 (C_{Het}-5), 21.4 (C_{CH3}).

2-(3-(M-TOLYL)UREA)THIAZOLE-4-CARBOXYLIC ACID. 0.45 ml (3.5 mmol, 0.46 g. ρ =1,033 g/ml) m-toluene isocyanate (1), 0.46 g (3.19 mmol) 2-aminothiazole-4-carboxylic acid (3), 10 ml DMFA and 0.45 g (3.26 mmol) of K_2CO_3 was obtained. 0.31 g of product (7) was obtained in 62% yield. . R_f = 0.77 (benzene: methanol–5:1). **^{1}H NMR (δ, m.u., CD_3OD):** 10.74 (1H,-COOH-H), 8.49 (1H,-NH-H), 7.69 (1H, c, H_{Het}-4), 7.25 (1H, c, H_{Ar}-6), 7.19 (1H, d, J=9.22, H_{Ar}-2), 7.09 (1H, t, J=7.80, H_{Ar}-5), 6.76 (1H, d, J=7.80, H_{Ar}-4), 2.30 (3H, H_{CH3}). **^{13}C NMR(CD_3OD):** 162.03 (C_{-COOH}), 160.66 (C_{Het}-2), 152.56 ($C_{-C=O}$), 142.46 (C_{Het}-4), 139.57 (C_{Ar}-3), 139.08 (C_{Ar}-1), 129.56 (C_{Ar}-5), 124.50 (C_{Ar}-2), 122.13 (C_{Ar}-4), 120.33 (C_{Ar}-6), 116.91 (C_{Het}-5), 21.89 ($C_{Alk-CH3}$). **IR (ν, cm $^{-1}$):** 3114 (C–H aryl), 2977 (CH_2 for the group), 676, 694 (C–S-C), 1614 (–C=N-), 1681 (>C=O), 676 (Ar (=C-H deform.t.), 1379 (–C–CH_3), 1121, 1107 (–C-OH).

1-(BENZO[d]THIAZOL-2-YL)-3-(M-TOLYL)UREA. 0.7 ml (5.4 mmol, 0.72 g, ρ =1.033 g/ml) of m-toluyl isocyanate (1), 0.81 g (5.4 mmol) of 2-aminobenzothiazole (4), 10 ml of DMFA and 0, 77 g (5.6 mmol) of K_2CO_3 were obtained. 1.27 g of product (8) was obtained in 83% yield. Liquid=340–342oC. Rf =0.76 (benzene: methanol – 5:1). 1HYaMR (m.u., CD3OD): 10.58 (1H, c, -NH), 8.82 (1H, c, -NH), 7.74 (1H, c, Het-H-4), 7.57 (1H, d, J=6.49, H_{Ar} –7), 7.28 (2H, m, H_{Het} –5.6), 7.23 (1H, d, H_{Ar}-3), 7.13 (2H, m, H_{Ar} –2,6), 6.77 (1H, d, J=7,53, H_{Ar} –4), 2.32 (3H, c, $H_{Alk-CH3}$). **^{13}C NMR (CD_3OD):** 160.73 (C_{Het}-1), 152.26 ($C_{-C=O}$), 139.66 (C_{Ar}-3), 139.13 (C_{Ar}-1), 132.78 (C_{Het}-7a), 129.60 (C_{Ar}-5), 126.54 (C_{Ar}-2), 124.53 (C-5), 120.70 (C_{Ar}-6), 120.32 (C_{Het}-4), 116.92 ($C_{hetaeryl}$-7), 21.91 (). **IR (ν, sm $^{-1}$): IR-(ν, sm $^{-1}$):** 3049 (C–H aryl), 728 (C–S-C), 1725 (>C=O), 690 (Ar (=C-H), 1451 (–C–CH_3), 1194, 1194 (–C-OH).

1-(6-NITROBENZO[d]THIAZOL-2-YL)-3-(m-TOLYL)UREA. 0.26 ml (2.03 mmol, 0.27 g., ρ =1.033 g/ml) m-toluyl isocyanate (1), 0.4 g (2.05 mmol) 2-amino-6-nitrobenzothiazole (5), 10 ml DMFA and 0.304 g (2.2 mmol) of K_2CO_3 were obtained. 0.4 g of product (9) was obtained in (59%) yield. Liquid=240–242oC. Rf =0.65 (benzene: methanol – 5:1). 1H NMR(m.u., CD3OD): 10.23 (1H, c, NH-), 8.86 (1H, d, J=2,47, $H_{hetaeryl}$-4), 8.22 (1H, dd, J=8.90, J=2.40, hetaeryl-6), 7.74 (1H, c, $H_{hetaeryl}$-7), 7.66 (2H, t, J=8.51, H_{Ar}-2,6), 7.24 (1H, t, J=7.80, H_{Ar}-5), 6.89 (1H, d, J=7.54, H_{Ar}-4), 2.18 (3H, c, $H_{Alk-CH3}$). **^{13}C NMR (CD_3OD):** 167.3 (C-1), 154.5 ($C_{C=O}$), 144.0 (C_{getr}-3a), 140.1 (C_{getr}-5), 139.7 (C_{Ar}-7a), 133.3 (C_{getr}-7), 129.9 (C_{Ar}-1), 125.3 (C_{Ar}-5), 122.7 (C_{Ar}-2), 121.5 (C_{Ar}-4), 119.7 (C_{getr}-6), 119.3 (C_{Ar}-6), 117.9 (C_{getr}-4), 21.3 (C_{CH3}-C). **IR (ν, sm^{-1}):** 3130 (C–H aryl), 747 (C–S-C), 1685 (>C=O), 642 (Ar (=C-H 1447 (–C–CH_3), 1549 (–C-NO_2).

Consulsion

The heterocycles of 2-aminothiazole scaffolds occupy a dominant part in organic/medicinal chemistry in relation to their reactivity and biological activity and mostly act as pharmacophores. The present review summarizes the literature reports of the various synthetic routes for 2-aminothiazole-containing molecules with four different biological activities (namely, anticancer, antioxidant, antimicrobial and anti-inflammatory activities). The presented information in this review is valuable for future innovation.

This review highlighted the recently synthesized 2-aminothiazole-containing compounds within the last thirteen years ago. Further, the synthetic strategies developed for the admission of the recent 2-aminothiazole derivatives (N-substituted, 3-substituted, 4-substituted, multi-substituted, aryl/alkyl substituents or acyl/other substituents) were presented. The reported literature revealed several synthetic pathways of those 2-aminothiazoles related to four different biological activities (anticancer, antioxidant, antimicrobial and anti-inflammatory activities). It is hoped that this review will be useful in displaying the rationalistic designs of 2-aminothiazole-based medical synthetic pathways.

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