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SYNTHESIS OF UNSYMMETRICAL MOCHIVENES BASED ON NUCLEOPHILIC COUPLING REACTIONS OF SECONDARY CYCLIC AMINES WITH O-TOLUYL ISOCYANATE

Kudratov G.N.[1], Ortikov I.S.[1], Elmuradov B.J.[1], Khudoyqulova R.Z.[1], Saitkulov F.E.[1]

[1] Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan

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Abstract

In the article, for the first time, the methods of synthesis of 1,3-substituted urea derivatives based on m-toluyl isocyanate and 2-aminothiazoles with different functional groups were explained, methods of obtaining 1,3-substituted urea derivatives, reaction mechanisms were studied in depth. The structure of the obtained substances has been proven by analysis of modern physical research methods.

Keywords: *synthesis of 1,3-substituted urea, m-toluyl isocyanate, 2-aminothiazoles, substituted urea derivatives, reaction mechanisms, structure, analysis, physical research method*

Introduction

Substituted ureas attract attracted attention due to its diverse applications in industry, technology, agriculture, and medicine (Kucheryavy V.I., Lebedev V.V., 1970; Vishnyakova T.P., Golubeva I.A., Glebova E.V., 1985; Mashkovsky M.D., 2012). They are widely used in as pesticides and plant growth regulators, are effective additives for hydrocarbon fuels for various purposes, oils, and polymeric materials; are used as medicines and dyes. To date, a huge amount of factual material has been accumulated on synthesis methods, properties and the use of substituted ureas. In 1982 a review has been published (Afanasyev V.A., Dzhamanbaev J.A., Zaikov G.E., 1982; Fukui H., Tanivoto F., Kitano H., 1965; Gerhardt G.W., 1968; Hoffman A.W., 1849; Davis T.L., Blanchard H.C., 1929; Pat. 2673859 USA, IPC 7 07 C 273/18, C 07 C 273/00. 1954; US3161677 (1964) (Schlatter R.); Chem. Abst., 1965; Kuliyev A.M., Abdinova A.B., 1958) examining methods synthesis, structure and properties of a specific class ureas – derivatives of hydrocarbons with urea fragments. It has been established that sulfonylureas, even at very low concentrations, are capable of inhibiting acetolactate synthetase, the first specific enzyme in chains of biosynthesis of isoleucine and valine, which leads to block cell division. Urea derivatives have different selectivity of action depending on

their buildings. Thus, sulfonylureas such as chlorsulforone act mainly on dicotyledons plants, and isoproturon acts on foxtail and selective for wheat. Due to the availability of a decently wide range of herbicide preparations Based on urea derivatives, it is possible to use them to control weeds in various crops. Most urea derivatives are soil herbicides. Of significant interest are 1,2,3-thiadiazolylureas, some of them have strong herbicidal effect and can be used as defoliants. From this group substances, the drug has found practical application Thidiazuron defoliant for fine fiber cotton, for which no other effective defoliants have yet been found. By mechanism of action this group of substances can be classified as cytokinins. Along with insecticides, fungicides and herbicides, zoocides were found among the derivatives. The most powerful zoocides are arylpyridyl ureas, of which practical use found N-nitrophenyl-N'-(pyridyl-3-methyl)-urea used as a dietary supplement (0.5% active ingredient). As zoocides Monoarylguanidines have also been proposed. In the first half of the twentieth century, the ability of antibacterial sulfonamide drugs to lower blood sugar was accidentally discovered. Then a targeted search for sulfonamide derivatives with a pronounced hypoglycemic effect began. It has since been synthesized three generations of sulfonylurea's. Despite significant advances in the field diabetology achieved over the past 20 years, diabetes continues to be a problem relevant in almost all countries of the world. To By 2025, there will be 380 million people with diabetes in the world. These numbers sounded at the World Diabetes Congress in Cape Town in 2006. It is predicted that by 2025 7% of the population will suffer from diabetes peace. Moreover, type 2 diabetes mellitus is predicted to scientists, will be 92–97%. Diabetes causes approximately 3.8 million deaths each year, and most of them die from its complications. U In 75% of patients with type 2 diabetes mellitus (DM2), the cause of high mortality is cardiovascular diseases, including coronary disease heart disease, stroke, atherosclerosis of peripheral arteries, arterial hypertension.

Methods and Results

For the synthesis of sulfonylureas, isocyanates are most often used, which, when interacting with sulfonamides, form sulfonylureas. To obtain isocyanates, the reaction of primary aliphatic or aromatic amines with phosgene, which is a chemical warfare agent. The original isocyanates are also compounds with increased toxicity. The reactivity of urea is typical for amides: both nitrogen atoms are nucleophiles, that is, urea forms salts with strong acids, nitrates to form Nnitrosourea, and halogenates to form Nhalogen derivatives. Urea alkylates, forming the corresponding N-alkylureas $RNHCONH_2$, interacts with aldehydes, forming derivatives of 1-amino alcohols $RC(OH)NHCONH_2$, in under harsh conditions, urea is acylated by acid chlorides of carboxylic acids to form ureides (N-acylureas). Sulfonylureas increase insulin secretion by stimulating beta cells pancreas (therefore they act until until the reserves of the insulin synthetic function of the pancreas are depleted). In As a result, the sensitivity of beta cells is restored and the number of insulin receptors increases. The main importance in the treatment of type 2 diabetes mellitus belongs to sulfonylurea drugs, which began to be used in clinical practice. practice since the mid-60s. A wide variety of hypoglycemic derivatives sulfonylureas are associated with radical differences at the phenolic ring. Sulfonylureas are divided into drugs 1 and 2 generation. Today, first generation sulfonylurea drugs (tolbutamide, chlorpropamide) are practically not used. Currently, there are several main methods for producing substituted ureas, Among them are the following: 1) Interaction of amino compounds with organic isocyanates; 2) Interaction of amines and alkyl halides with alkali metal cyanates; 1) Interaction of primary and secondary amines with phosgene; 2) Interaction of amines with urea and nitrosourea; 3) Interaction of urea with various connections; 4) Carbonylation of amines to substituted ones urea; 5) Synthesis of substituted ureas from amides acids (Hoffmann rearrangement).

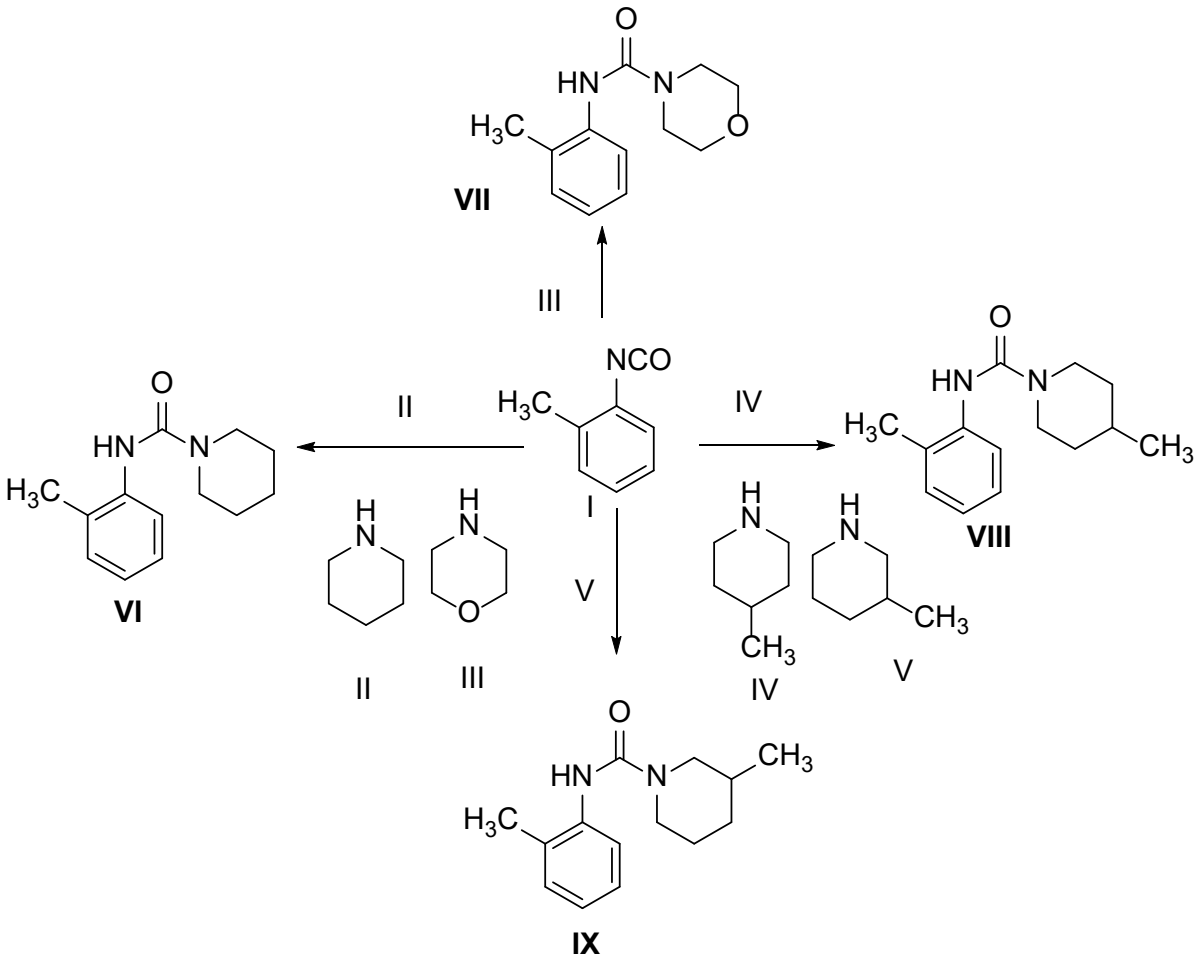
One of the simplest methods for producing urea derivatives is the interaction of the amine with isocyanates. Isocyanates are organic compounds containing the functional group -N = C = O. Isocyanates, being heterocumulenes, are active electrophilic reagents. When interacting with primary and second-

ary amines, they form substituted ureas, with alcohols they form carbamates (urethanes), and are hydrolyzed with water to amines and carbon dioxide.

The most common synthesis method isocyanates – reaction of amines with phosgene (phosgenation of amines), the reaction occurs in an inert solvent through the intermediate formation of carbamoyl chlorides. The reaction occurs both in organic solvents and without them. The process temperature depends on the structure of the starting isocyanates and amine. In

Tertiary amines or organic tin compounds can be used as catalysts. At When the process is carried out correctly, the product is obtained in almost quantitative yield. The isocyanates required for this method are obtained from reactions of the corresponding amines with phosgene, such as usually at elevated temperatures. This method is the main industrial method for the synthesis of isocyanates. Sulfonylisocyanates are prepared similarly. Other acyl isocyanates with better yields are formed from amides and oxalyl chloride. On the basis of various solvents, we continued our scientific work and synthesized urea derivatives based on toluene isocyanates. The reaction scheme is expressed as follows.

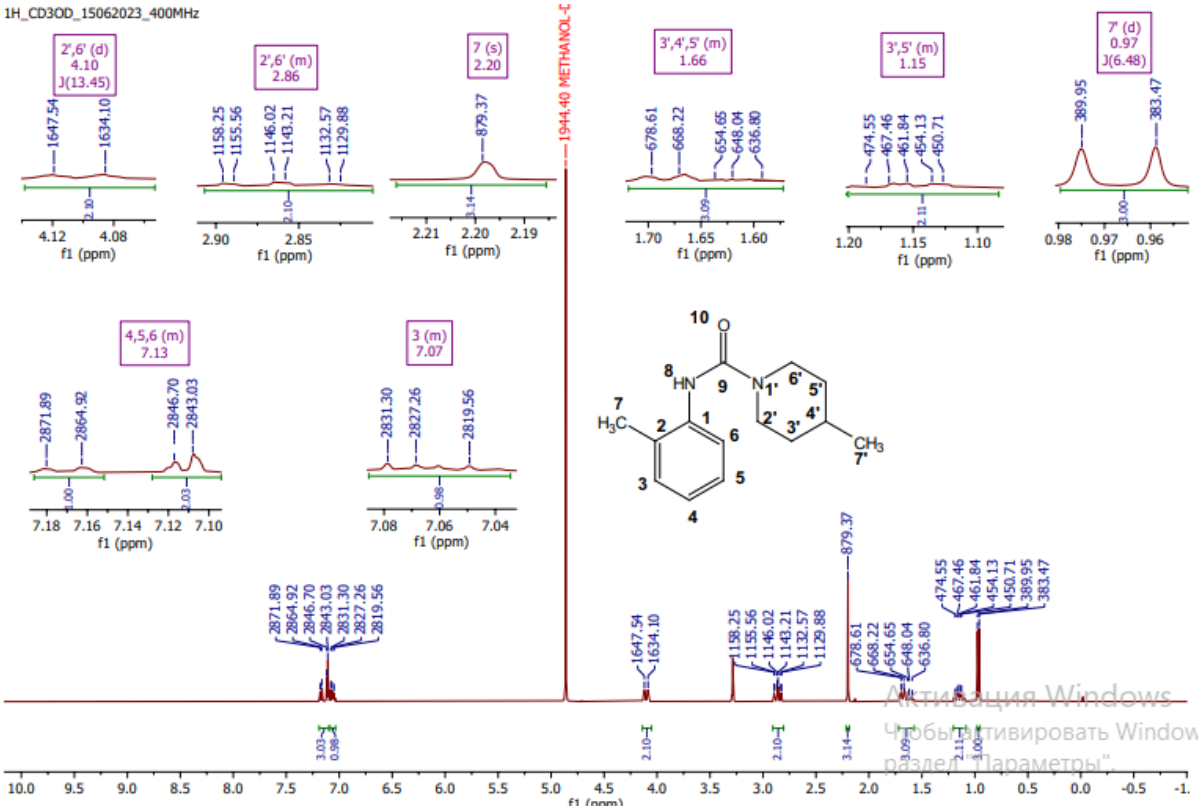
Figure 1.



1,3-substituted aryl-heteryl urea derivatives were synthesized in good yields. -IR, ^{1}H-NMR, ^{13}C-NMR spectra of the obtained substances were analyzed.

The structure of 8 substance molecules was determined using ^{1}H NMR physical research methods (Fig. 1)

Figure 1. *8 substance molecules was determined using ^1H NMR*



Experimental Part

Synthesis of N-(toluyl)piperidine-1-carboxamide.

0.385 ml (3 mmol, 0.413 g, r=1.073 g/ml) of o-toluyl isocyanate, 0.383 ml (3.88 mmol, 0.33 g, ρ=0.862 g/ml) of piperidin were added to a 100 ml round-bottom flask. 10 ml of acetone was poured into the flask and mixed on a magnetic stirrer. After the substances were completely dissolved, 0.414 g (3 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, extracted with K_2CO_3 and dried to give 0.487 g. (73%) product was obtained. The ^1H NMR-spectrum data of substance I presented below fully prove the structure of this substance: 1.63(6H, m, Het-C-H-3′,4′,5′), 2.20(3H, c, Het-CH_3), 3.47 (4H, m, Het-C-H-2′, 6′), 7.06(1H, м, Ar-4), 7.11(2H, d, J=2.9, Ar-5,6), 7.17(1H, d, Ar-3). **^{13}C NMR (CD_3OD):**157.27, 137.26, 134.31, 130.08, 126.63, 125.87, 47.03, 45.04, 25.67, 24.26, 16.83.

Synthesis of N-(toluyl)morphaline -4-carboxamide

0.247 ml (2.65 mmol, 0.353 g, r=1.073 g/ml) o-toluyl isocyanate, 0.3 ml (3.32 mmol, 0.3 g, ρ=1.007 g/ml) morphalin 10 ml acetone 0.445 g (2.65 mmol) K_2CO_3 was obtained. 0.36 g product was obtained with 62% yield. ^1H NMR **($CDCl_3$):** 2.21(3H, d, J=0.9, Ar-CH_3), 3.48(4H, м, Het-C-H-2′,6′),3.69(4H, м, Het-C-H-3′,5′), 7.08(1H, d, J_1=7.4, J_2=5.3, Ar-4), 7.13(2H, м, Ar-5,6), 7.19(1H, d, J=7.6, Ar-3). **^{13}C NMR (CD_3OD):**157.46, 136.89, 134.33, 130.16, 126.60. 125.69, 66.38, 48.31, 44.30, 16.81.

Synthesis of 4-methyl-N-(toluyl) piperidine-1-carboxamide.

0.37 ml (3 mmol, 0.398 g, r=1.073g/ml) o-toluene isocyanate, 0.442 ml (3.7mmol), 0.37 g, ρ=0.838g/ml) 4-methylpiperidine 10 ml acetone 0.414g (3 mmol) of K_2CO_3 was obtained. 0.622 g product was obtained with 89% yield. **^{1}H NMR ($CDCl_3$):** 0.97(3H, d, J=6.5, Het-CH_3), 1.15(2H, м, Het-C-H-3′,5′), 1.66(3H, м, Het-C-H-3′,4′,5′), 2.20(3H, c, Ar-CH_3), 2.86(2H, м, Het-C-H-2′,6′), 4.10(2H, d, J=13.4, Het-C-H-2′,6′), 7.07(1H, м, Ar-3), 7.13(3H, м, Ar-4,5,6).**^{13}C NMR (CD_3OD):**

157.25, 137.24, 134.31, 130.08, 126.63, 125.88, 125.47, 47.03, 44.43, 33.99, 30.98, 20.94, 16.83.

Synthesis of 3-methyl-N-(toluyl) piperidine-1-carboxamide

0.343ml (2.76 mmol, 0.343g, ρ=1.073g/ml) o-toluyl isocyanate, 0.405 ml (3.45 mmol), 0.342g, ρ=0.845g/ml) 3-methylpiperidine, 10 ml acetone 0.35g (2.76 mmol) of K_2CO_3 was obtained. 0.59 g product was obtained with 96% yield. **^{1}H NMR ($CDCl_3$):**0.93(3H, , J=6.7, Het-CH_3), 1.16(1H, м, Het-C-H-4′), 1.62(1H, м, Het-C-H-4′,5′,5′), 1.85(1H, м, Het-C-H-3′), 2.53(1H, м, Het-C-H-2′), 2.85(1H, м, Het-C-H-2′), 3.99(2H, т, J=13.0), 7.09(3H, м, Ar-4,5,6), 7.15(1H, d, J=7.7, Ar-3). **^{13}C NMR (CD_3OD):**157.07, 137.24, 134.17, 130.15, 126.59, 125.46, 51.63, 44.64, 32.98, 31.15, 25.14, 18.25, 17.17.

Conclusion

Outlined basic methods of obtaining zameshchennyx urea, kak semi-products and synthesis of biologically active preparations (herbicides, fungicides, root preparations, saccharosnijayuschich preparations and others). Opredeleny sposoby polucheniya naibolee dostupnyx aryl-, heteroarylurea. Named basic principle synthesis of zameshchennyx urea, used in the synthesis of biologically active compounds.

References

Kucheryavy V. I. Synthesis and application of carbamide. / V. I. Kucheryavy, V.V. Lebedev. Leningrad: Khimiya Publ., 1970. – 448 p.

Vishnyakova T. P., Substituted urea. Synthesis methods and applications / T. P. Vishnyakova, I. A. Golubeva, E.V. Glebova // Successes of Chemistry. 1985. - 54(3). – P. 429-449.

Mashkovsky M. D. Medicines / M. D. Mashkovsky. – Moscow: 2012.

Afanasyev V. A. Derivatives of Hydrocarbons with carbamide fragments / V. A. Afanasyev, Zh. A. Jamanbaev, G. E. Zaikov // Successes of Chemistry. 1982.– 51(4).– 677 p.

Fukui H. / H. Fukui, F. Tanivoto, H. Kitano. //Bull. Chem. Soc. Japan. 1965.– V. 38.– 1586 p.

Gerhardt G. W. / G.W Gerhardt. // J. Pract. Chem. 1968.– B. 38.– 77 p.

Hoffman A. W. / A. W. Hoffman // Ann. Chem. 1849.– B. 70.– 129 p.

Davis T. L., Blanchard H. C. / T. L. Davis, H. C. Blanchard. // J. Amer. Chem. Soc. 1929.– Vol. 51.– 1790 p.

Pat. 2673859 США, МПК7 C 07 C 273/18, C 07 C 273/00. Production of urea derivatives / John Kenson Simons Allied Chemical & Dye Corporation –№ 185167; заявл. 15.09.1950; опубл. 30.03.1954; Chem. Abst., 1955.– Vol. 49.– 4015 p.

US3161677 (1964) (Schlatter R.); Chem. Abst., 1965.– Vol. 62.– 7649 p.

Kuliev A. M. (A) M. Kuliev, A. B. Abdinova. // UCH. Notes On Azerb. UN-Ta, 1958.– T. 5.– 47 p.

US2849488 (1958) (Ambelang I. C., Massie G.). Chem. Abst., 1959.– Vol. 53.– 3069 p.

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Contact: fsaitkulov@bk.ru