тезу і створення нових біологічно активних сполук та фармацефтичних препаратів: тези доп. Нац. науково-технічної конф. з міжн. участю. – Львів, 2008. – С. 68.

8. Gulgule S. Isocoumarins. IX. 3-Phenylisocoumarins and Synthesis of 3-Phenyl-3,4-dihydroisocoumarins, 3-Phenylisochromenes and 3-Phenylisochromans / S. Gulgule, R.N. Usgaonkar // J. Indian Chem. Soc. – 1971. – Vol. 48, № 8. – P. 707–712.

9. Legrand L. Heterocyclic sulfur compounds. XIII. 1-Thio, 2-thio and 1,2-ditihioisocoumarins / L. Legrand, N. Lozac'h // Bull. Soc. Chim. France. – 1964. – № 8. – P. 1787–1793.

10. Hussain A., Rama N.H., Malic A. Synthesis of Some New 3-(Bromophenyl)isocoumarins and and Their Conversion to (dl)-3,4-Dihydroisocoumarins / A. Hussain, N.H. Rama, A. Malic // Indian J. Chem., Sect. B. – 2001. – Vol. 40B, № 5. – P. 372–376.

11. Шабликіна О.В. 3-Гетарил(арил)кумарини та ізокумарини. Синтез і властивості: дис. ... канд. хім. наук: 02.00.03 / О.В. Шабликіна; КНУ імені Тараса Шевченка. – Київ, 2006. – 174 с.

Надійшла до редколегії 30.05.13

О. Шаблыкина, канд. хим. наук,
КНУ имени Тараса Шевченко, Киев
С. Чумаченко, инженер,
Институт биоорганической химии и нефтехимии НАН Украины, Киев
В. Ищенко, канд. хим. наук,
В. Хиля, д-р хим. наук, чл.-кор. НАН Украины
КНУ имени Тараса Шевченко, Киев

СИНТЕЗ 3-АРИЛИЗОКУМАРИНОВ С СУЛЬФАМИДНЫМИ ГРУППАМИ

Исследовано взаимодействие 3-арилизокумаринов с хлорсульфоновой кислотой и предложен метод введения в молекулу 3-арилизокумарина фармакофорного фрагмента сульфамида.

Ключевые слова: изокумарины (1Н-изохромен-1-оны), хлорсульфирование, сульфонамиды.

O. Shablykina, PhD,
Taras Shevchenko National University of Kyiv, Kyiv
S. Chumachenko, engineer,
Institute of Bioorganic Chemistry and Petrochemistry of National Academy of Sciences of Ukraine, Kyiv
V. Ishchenko, PhD, V. Khilya, Professor
Taras Shevchenko National University of Kyiv, Kyiv

SYNTHESIS OF 3-ARYLISOCOUMARINES WITH SULFAMIDE GROUPS

Interaction of 3-arylisocoumarines and Chlorosulfonic acid was investigated. Method of creation of pharmacophore sulfamide fragment into the 3-arylisocoumarine molecule was proposed.

Key words: isocoumarins (1H-isochromen-1-ones), chlorosulfonation, sulfonamides.

УДК 547.759.4

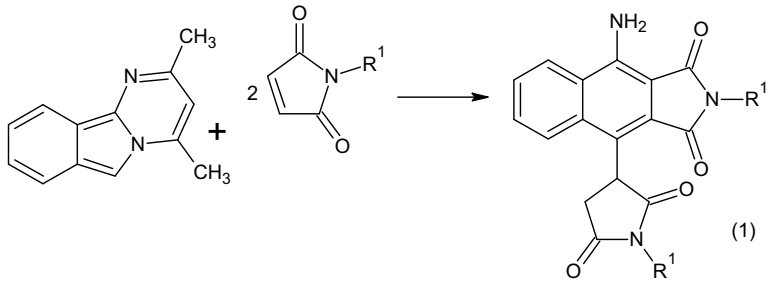
S. Krykun, Student, T. Yegorova, PhD, I. Levkov, PhD, Z. Voitenko, Professor,
Taras Shevchenko National University of Kyiv, Kyiv

SYNTHESIS OF 4-AMINO-BENZO[*f*]ISOINDOLE DERIVATIVES BY REACTION 1-AMINO-2-ARYLISOINDOLES WITH MALEIMIDES

Investigated the reactivity of 1-amino-2-arylisoindoles, the main tautomeric forms for which is imine form. It is shown that the reaction of 1-amino-2-arylisoindoles with maleimides produces derivatives of 4-amino-benzo[f]isoindole. Developed two new methods for the synthesis of fluorescent derivatives of 4-amino-benzo[f]isoindole, which have several advantages relative described earlier in the literature: reaction speed, simple selection of products with high purity, better outputs.

Key words: isoindole, rearrangement, bis-Michael adduct.

Introduction. Derivatives of 4-amino-benzo[*f*]isoindole (1), also known as rearrangement products of the second type are object of interest from both practical and fundamental points of view. Thus, compounds containing succinimide fragment show diversified biological activity, including a-1A adrenergic receptor antagonist, androgen receptor antagonist, anxiolytic, antiviral, antibacterial, anti-inflammatory, antitumor, hypolipidaemic and fungicidal properties [1–6]. Compounds with isoindole core should have antidepressant and anorexia effect [7, 8]. Compounds of type (1) have fluorescent properties [9, 10]. Methods of synthesis (1) are interesting from the perspective of theoretical chemistry. The formation of (1) was first shown by our research group for example 2,4-dymetylpirimido[2,1-*a*]isoindole (Scheme 1), where (1) was formed as a result of rearrangement of *exo*-adduct Michael-Diels-Alder reaction [9].



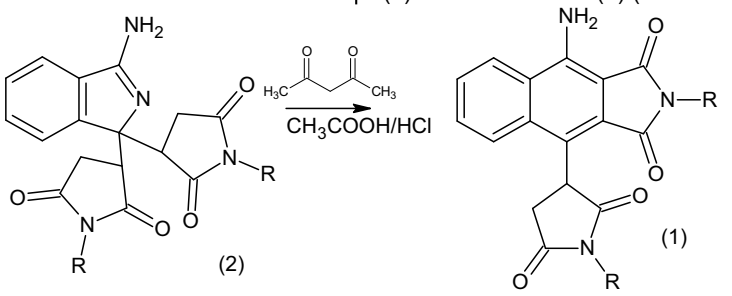
Scheme 1. Interaction 2,4-dymetylpirimido[2,1-*a*]isoindole with maleimides

Another known method of synthesis of (1) is the interaction of *bis*-Michael adduct (2) of acetylacetone in acetic acid saturated with hydrogen chloride (Scheme 2). [10]

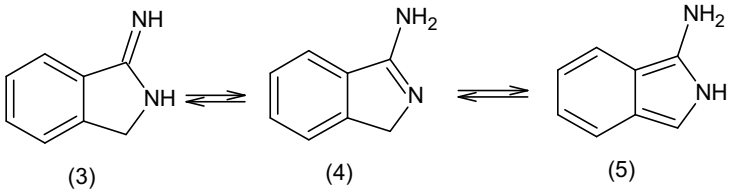
Results and discussion. This work is devoted to the study of the reactivity of substituted 1-aminoisoindoles in reactions with maleimides and synthesis of (1).

Previously, our research group has shown that in the reaction of 1-unsubstituted aminoisoindoles [11] and its analogue – 1-ethoxyisoindole [12] with maleimids as a result of a number of successive transformations *bis*-Michael adducts are formed, because for the Curtine-Hammet principle it is needed only a small amount of initial

reactants in equilibrium system for the successful completion of the reaction, and in case of 1-ethoxyisoindole depending on the substituent at the nitrogen atom in maleimide can be obtained *mono*- or *bis*-Michael adducts or there mixtures. In case of 1,2-dyarylisoindoles with fixed isoindole fragment interaction with maleimides follows the classical scheme and the rearrangement does not occur, but depending on reaction conditions Diels-Alder or Michael adducts are formed[13]. Effect of substituents in the second position of 1-aminoisoindoles has not been yet studied. As you know, isoindole derivatives have a special type of tautomerism - isoindolo-isoindolenine tautomerism [14]. In case of the second substituent in position 1 aminoisoindole loses the opportunity to be in isoindolenine tautomeric form (4), but the basic form remains isoindole (5) and imine forms (3) (Scheme 3).

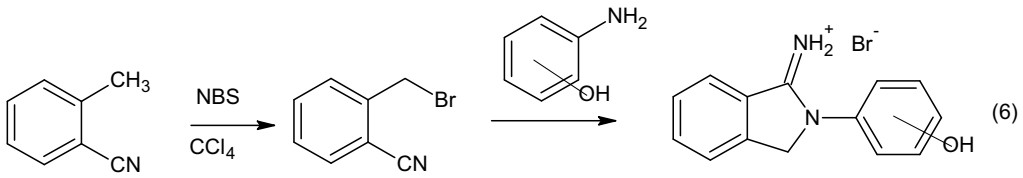


Scheme 2. Regrouping bis-Michael adduct



Scheme 3. Tautomeric forms

Source 1-amino-2-arylisoindoles (6) were synthesized from 2-methylbenzonitrile and the corresponding *ortho*-, *meta*- and *para*-aminophenols. It has been shown that reaction has good yields for *ortho*-and *meta*-substituted aminophenols, but in case of *para*-substituted aminophenol synthesis was ineffective because of formation of by-products, most likely oxidation products. Therefore, further work was carried on *ortho*-and *meta*-substituted aminophenols and corresponding isoindoles (Scheme 4).

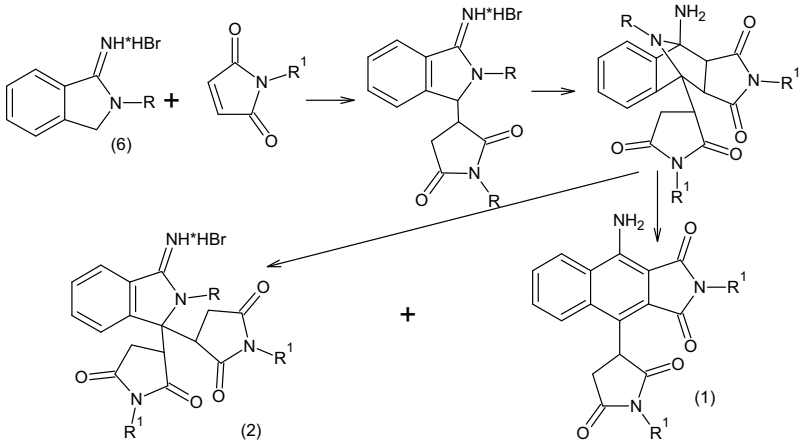


Scheme 4. Synthesis of isoindoles

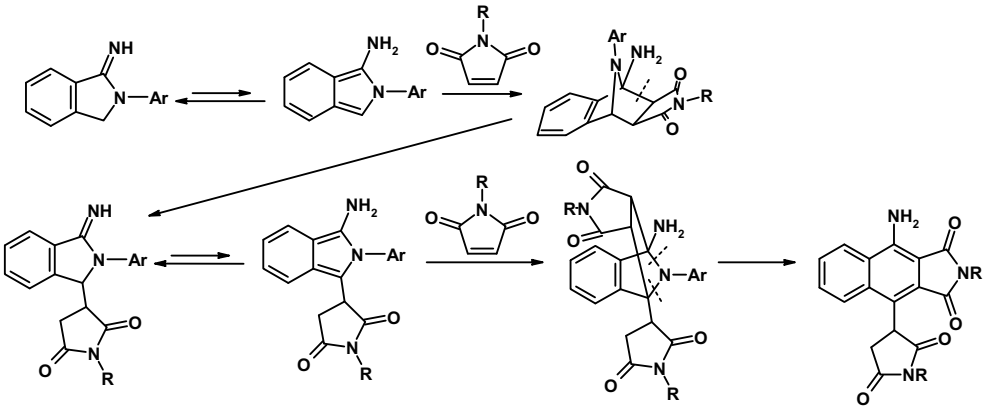
While studying the reaction between (6) and maleimides in methanol at room temperature (conditions similar to the reaction of unsubstituted aminoisoindoles in [11]) in addition to the expected product (2) was obtained also compound (1), the ratio of the reaction products was about 1:1 (Scheme 5). Reaction in isopropyl alcohol gives same result. Since the initial isoindoles were as hydrobromide, the base form was generated *in situ* by addition of triethylamine. The formation of the reaction products can be imagined as successive attacks by Michael and Diels – Alder reaction followed by rearrangement in 7-azanorbornen system. There are two different rearrangement: 1) bond breaking in azanorbornen fragment to form compound (2) is similar to such as in case of unsubstituted 1-aminoisoindoles 2) rearrangement by scheme 6, resulting in forming compound (1) (Scheme 6). In fact there are two parallel reactions.

By selecting of the reaction conditions was shown the possibility of kinetic control of the reaction. A number of conditions were investigated and selected the most promising to shift the equilibrium toward the formation of product (1). Compounds (1) were obtained by the reaction at low temperature (~ 5 ^{0}C) in acetonitrile. In this case, the main problem was the reaction speed – 5–7 days and relatively low yield (30%). It was also shown that a slight increase in temperature does not significantly change result of the reaction – at room temperature in acetonitrile reaction time remained within 5–7 days. Significant problem is the solubility of starting materials at low temperatures, resulting in significantly increased reaction time. The same can be explained for relatively low output, which may be slightly increased by the elongation of reaction time, however, this approach is not effective.

Therefore, it was tried to use relatively low-boiling solvents, thereby controlling the reaction temperature. Reaction in dichloromethane gave the opportunity to obtain pure product (2). This also significantly reduced reaction time to 4-5 hours. Control was carried out by TLC, whereas identification was carried out by 1H NMR. Previously, our research group has developed clear criteria for both possible products. Thus, for (2) are characteristic signals of succinimide protons 1.2–1.4 (J = 6.0, 18.8 Hz); 2.4–2.8 (9.2, 18.8 Hz) and 4.6-4.8 (6.0, 9.2 Hz) for protons Ha, Hb and Hc, respectively. For (1) type are characteristic signals of protons in succinimide 2.8–3.4 (J = 7.2, 17.6 Hz; J = 9.2, 17.6 Hz) and 5.2–5.4 (J = 7.2, 9.2 Hz). Typical spectras of corresponding adducts are shown in Fig. 1.



Scheme 5. General reaction scheme



Scheme 6. The proposed reaction mechanism

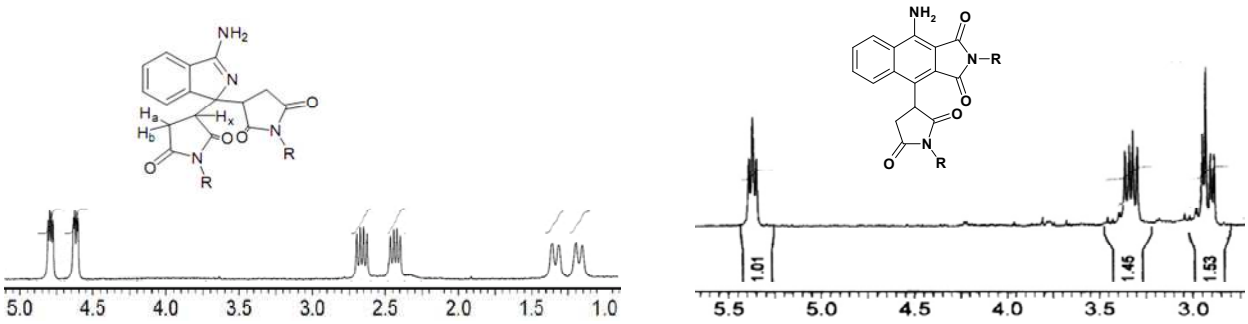


Figure 1. *Bis*-adduct Michael adduct; adduct of rearrangement of the second type

Conclusions. Investigated the reactivity of 1-amino-2-arylisoindoles, the main tautomeric forms for which is imine form. It is shown that the reaction of 1-amino-2-arylisoindoles with maleimides forms derivatives of 4-amino-benzo[*f*]isoindole. Developed two new methods for the synthesis of fluorescent derivatives of 4-amino-benzo[*f*]isoindole, which have several advantages relative described earlier in the literature – reaction speed, simple selection of products with high purity, better outputs.

Experimental part. The ^{1}H NMR and ^{13}C NMR spectra (400.396 MHz) were recorded whit a Varian Mercury 400 whit TMS as internal standard. IR spectra were recorded with FT IR spectrometer Perkin Elmer BXII. Elemental analyses were realized whit a Carlo Erba analyser.

Methods for synthesis of 3-amino-2-(2-hydroxyphenyl)-isoindol bromyd.

To 0.5 mol 2-bromobenzonitrile in 50 ml isopropyl alcohol added 0.5 mol 2-aminophenol, mixture was refluxed for 2 hours. After that precipitate formed was filtered off and recrystallized from isopropyl alcohol.

3-amino-2-(2-hydroxyphenyl)-isoindol bromyd

Yield 75%. ^{1}H NMR (DMSO d-6, 400 MHz), δ: 5,3 (s, 2*H*), 6.98 (d, *J* = 7.5 Hz, 1*H*), 6.97 (d, *J*=7.5 Hz, 1*H*),7.04 (d, *J*=7.5 Hz, 1*H*), 7.08 (s, 1*H*), 7.44 (t, *J* = 8.0 Hz, 1*H*), 7.84 (t, *J* = 8.0 Hz, 1*H*), 9.18 (s, 2*H*), 10.05 (bs, 1*H*)

Methods of synthesis in acetonitrile.

Dissolved 4 mmol N-substituted aminoisoindole and 5 mmol of base (triethylamine) in 15 ml of acetonitrile, a solution of 8 mmol corresponding maleimide. Stired the reaction mixture to dissolve the reactants. Leaved the solution for 3-4 days at room temperature with stirring. The crystalline precipitate formed was filtered off and recrystallized from isopropyl alcohol.

Methods of synthesis in dichloromethane.

Dissolved 4 mmol of N-substituted aminoisoindole and 5 mmol of base (triethylamine) in 25 ml of dichloromethane, a solution of 8 mmol corresponding maleimide. Reaction mixture was refluxed at the boiling point of dichloromethane for 5 hours. The crystalline precipitate formed was filtered off and recrystallized from isopropanol.

4-Amino-9-(2,5-dioxo-1-phenylpyrrolidin-3-yl)-1-phenyl-benzo[f]isoindole-1,3-dione.

Yield 75%. ^{1}H NMR (DMSO d-6, 400 MHz), δ.: 3.06 (dd, *J* = 7.2, 17.6 Hz, 1*H*), 3.36 (dd, *J* = 9.2, 17.6 Hz, 1*H*), 5.46 (dd, *J* = 7.2, 9.2 Hz, 1*H*), 7.32 (d, *J* = 7.6 Hz, 2*H*), 7.40–7.54 (m, 8H), 7.58 (s, NH2), 7.78 (t, *J* = 7.8 Hz, 1*H*), 7.87 (t, *J* = 7.8 Hz, 1*H*), 8.48 (d, *J* = 7.8 Hz, 1*H*), 8.58 (d, *J* = 7.8 Hz, 1*H*).

^{13}C NMR (DMSO d-6, 100 МГц), δ: 37.39, 39.01, 101.65, 122.81, 125.37, 125.51, 126.29, 126.47, 127.78, 127.89, 128.49, 128.53, 128.88, 129.53, 129.68, 131.01, 132.69, 133.72, 136.80, 146.00, 167.64, 168.84, 176.13, 177.89.

IR (KBr):. 3428, 3334, 3066, 1698, 1638, 1494, 1370, 1164,764 см$^{-1}$

Elemental analysis, calculated $C_{28}H_{19}N_3O_4$: C, 72.88; H, 4.15; N, 9.11;found: C, 72.83; H, 4.11; N, 9.17;

4-Amino-9-(2,5-dioxo-1-(p-methoxyphenyl)pyrrolidin-3-yl)-1-(p-methoxyphenyl)benzo[f]isoindole-1,3-dione.

Yield 70%. ^{1}H NMR (DMSO d-6, 400 MHz), δ: 8.58 (d, 1*H*), 8.47 (d, 1*H*), 7.86 (t, 1*H*), 7.78 (t, 1*H*), 7.54 (bs, 2*H*), 7.36 (d, 2*H*), 7.20 (d, 2*H*), 7.05 (m, 4*H*), 5.41 (dd, 1*H*), 3.91 (s, 3*H*), 3.89 (s, 3*H*), 3.17 (dd, 1*H*), 3.02 (dd, 1*H*).

Elemental analysis, calculated $C_{30}H_{23}N_3O_6$: C, 69.09; H, 4.45; N, 8.06; found: C, 69.20; H, 4.52; N, 7.95

4-Amino-9-(2,5-dioxo-1-(2,3-dimethylphenyl)pyrrolidin-3-yl)-1-(2,3-dimethylphenyl)benzo[f]isoindole-1,3-dione.

Yield 75%. ^{1}H NMR (DMSO d-6, 400 MHz), δ: 8.53 (d, 1*H*), 8.48 (d, 1*H*), 7.79 (t, 1*H*), 7.72 (t, 1*H*), 7.45 (s, 2*H*), 7.2–7.3 (m, 6*H*), 5.58 (dd, 1*H*), 3.41 (dd, 1*H*), 2.85 (dd, 1*H*), 2.2–2.3 (m, 12*H*).

Elemental analysis, calculated C32H27N3O4: C, 74.26; H, 5.26; N, 8.12; found: C, 74.32; H, 5.28; N, 8.05

4-Amino-9-(2,5-dioxo-1-benzylpyrrolidin-3-yl)-1-benzylbenzo[f]isoindole-1,3-dione.

Yield 72%. ^{1}H NMR (DMSO d-6, 400 MHz), δ,: 8.52 (d, 1*H*), 8.45 (d, 1*H*), 7.81 (t, 1*H*), 7.74 (t, 1*H*), 7.25–7.50 (m, 12*H*), 6.13 and 5.34 (dd, 1*H*), 4.71 (m, 4*H*), 3.24 (dd, 1*H*), 2.83 (dd, 1*H*).

Elemental analysis, calculated C30H23N3O4: C, 73.61; H, 4.74; N, 8.58; found: C, 73.82; H, 4.76; N, 8.51

4-Amino-9-(2,5-dioxo-1-α-naphtylpyrrolidin-3-yl)-1-α-naphtylbenzo[f]isoindole-1,3-dione.

Yield 65%. ^{1}H NMR (DMSO d-6, 400 MHz), δ: 8.45 (d, 1*H*), 8.38 (d, 1*H*), 7.67 (t, 1*H*), 7.60 (t, 1*H*), 7.3–7.6 (m, 16*H*), 5.24 (m, 1*H*), 3.58 (dd, 1*H*), 3.27 (dd, 1*H*).

Elemental analysis, calculated C32H24N3O4: C, 76.99; H, 4.13; N, 7.48; found: C, 77.10; H, 4.19; N, 7.40

References

1. Snyder S.H. Drugs and the Brain / S.H. Snyder. – Scientific American Library: New York, 1986. – 228 p.

2. Crider A. M. Synthesis and anticancer activity of nitrosourea derivatives of phensuximide / A. M. Crider, T. M. Kolczynski, K. M. J. Yates // Med. Chem. – 1980 – V. 23. – P. 324–326.

3. Ando Y. Thalidomide Metabolism by the CYP2C Subfamily / Y. Ando, E. Fuse, W. D. Figg // Clin. Cancer Res. – 2002 – V. 8. – P. 1964–1973.

4. Freiberg C. Discovering the Mechanism of Action of Novel Antibacterial Agents through Transcriptional Profiling of Conditional Mutants / C. Freiberg, H. P. Fischer, N. A. Brunner // Antimicrob. Agents Chemother. – 2005 – V. 49. – P. 749 –759.

5. Andrimid, a new peptide antibiotic produced by an intracellular bacterial symbiont isolated from a brown planthopper / A. Fredenhagen, S. Y. Tamura, P. T. M. Kenny et al. // J. Am. Chem. Soc. – 1987. – V. 109. – P. 4409–4411.

6. Adamantyl maleimide induced changes in adhesion molecules and ROS are involved in apoptosis of human gastric cancer cells / J. J. Wang, T. Y. Liu, P. H. Yin et al. // Anticancer Res. – 2000. – V. 20, № 5A. – P. 3067–3073.

7. Pharmacology and biochemical profile of a new anorectic drug: mazindol / M.O. Carruba, F. Zambotti, L. Vicentini et al // Garattini S. Central Mechanisms of Anorectic Drugs / Garattini S. Samanin R (eds). –New York: Raven Press, 1978. – P. 145–164.

8. Benzo- and cyclohexanomazindol analogues as potential inhibitors of the cocaine binding site at the dopamine transporter / W.J. Houlihan, U.F. Ahmad, J. Koletar et al. // J. Med. Chem. – 2002. – V. 45, №19. – P. 4110–4118.

9. Benzo[*f*]isoindole derivatives from cycloaddition reaction of 2,4-dimethylpyrimido[2,1-a]isoindole and aleimides / Z. V. Voitenko, O. A. Pokholenko, O. T. Ilkun et al. // C. R. Chimie. – 2006. – V. 9. – P. 1482–1487.

10. 4-Amino-benzo[*f*]isoindole derivatives: synthesis and fluorescence properties / I. V. Levkov, Z. V. Voitenko, O. A. Zaporozhets et al. // J. Chem. Res. – 2011. – № 4. – P. 209–213.

11. The Curtin-Hammett principle in action: 1-amino-3H-isoindole in cycloaddition reactions / I. V. Levkov, O. V. Turov, O. V. Shishkin et al. // Tetrahedron. – 2010. – V. 66, № 2. – P. 508–512.

12. Reaction of 1-ethoxyisoindole with maleimide and its derivatives / I. V. Levkov, S. Cassel, Z. V. Voitenko et al. // Heterocycles. – 2012. – № 7. – P. 1671–1681.

13. 2-Substituted-isoindoles: a novel synthetic route and a study of the Diels-Alder and Michael reactions / Z. V. Voitenko, V. V. Sypchenko, I. V. Levkov et al. // J. Chem. Res. – 2011. – № 11. – P. 615–618.

14. Veber D. F. 1-Arylisoindoles / D. F. Veber, W. Lwowski // J. Am. Chem. Soc. – 1963. – V. 85, P. 646–647.

Надійшла до редколегії 06.06.13

С. Крикун, студент, Т. Єгорова, канд. хім. наук, І. Левков, канд. хім. наук, З. Войтенко, д-р хім. наук,
КНУ імені Тараса Шевченка, Київ

СИНТЕЗ ПОХІДНИХ 4-АМІНО-БЕНЗО[*F*]ІЗОІНДОЛУ РЕАКЦІЄЮ 1-АМІНО-2-АРИЛІЗОІНДОЛІВ З МАЛЕЇНІМІДАМИ

Досліджено реакційну здатність 1-аміно-2-арилізоіндолів, для яких переважає імінна таутомерна форма. Було показано, що реакція 1-аміно-2-арилізоіндолів із малеїнімідами приводить до утворення похідних 4-аміно-бензо[f]ізоіндолу. Розроблено 2 методи синтезу флуоресцентних похідних 4-аміно-бензо[f]ізоіндолу, які мають декілька переваг порівняно із описаними раніше: швидкість реакції, простота виділення та очистки, кращі виходи.

Ключові слова: ізоіндол, перегрупування, біс-адукт Міхаеля.

С. Крикун, студент, Т. Егорова, канд. хим. наук, И. Левков, канд. хим. наук, З. Войтенко, д-р хим. наук,
КНУ имени Тараса Шевченко, Киев

СИНТЕЗ ПРОИЗВОДНЫХ 4-АМИНО-БЕНЗО[*F*]ИЗОИНДОЛА РЕАКЦИЕЙ 1-АМИНО-2-АРИЛИЗОИНДОЛОВ С МАЛЕИНИМИДАМИ

Исследована реакционная способность 1-амино-2-арилизоиндолов, для которых преобладает иминная таутомерная форма. Показано, что реакция 1-амино-2-арилизоиндолов с малеинимидами приводит к образованию производных 4-амино-бензо[f]изоиндола. Разработаны 2 метода синтеза флуоресцентных производных 4-амино-бензо[f]изоиндола, которые имеют несколько преимуществ по сравнению с описанными ранее: скорость реакции, простота выделения и очистки, лучшие выходы.

Ключевые слова: изоиндол, перегруппировка, бис-аддукт Михаэля.