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*N.V. Smetanin [a], S.A. Varenichenko [a], A.V. Mazepa [b], O.K. Farat [a], A.V. Kharchenko [a], V.I. Markov [a]*

# ATOM-ECONOMIC MICHAEL REACTION BETWEEN HYDROACRIDINES AND ARYLMALEIMIDES WITHOUT CATALYST/ADDITIVE

**[a] Ukrainian State University of Chemical Technology, Dnipro, Ukraine**
**[b] A.V. BogatskyPhysico-Chemical Institute of the National Academy of Sciences of Ukraine, Odessa, Ukraine**

Previously unknown spiroderivatives of 3,1-benzoxazines were synthesized by the reaction of anthranilic acid with cyclic ketones. The interaction of 3,1-spirobenzoxazines with Vilsmeier-Haack reagent ($POCl_3$ ($PBr_3$)/DMF), depending on the amount of formulation agent, leads to the formation of hydroacridones or hydroacridines. Under catalyst- and additive-free conditions, N-arylmaleimides, like Michael's acceptors, are added to the hydroacridines in DMSO to form the corresponding adducts. The reaction proceeds stereoselectively with the formation of a mirror pair of diastereomers, if the products have only two chiral centers. In the presence of three chiral centers in the structure of Michael's adducts, the reaction is not stereoselective. The reaction proceeds by the $sp^3$ hybrid carbon atom under non-catalytic conditions due to the imin-enaminetautomerism of chloro(bromo)hydroacridines. The presented reaction can also be considered as an effective atom-economical aza-ene reaction, which fully meets today's requirements for eco-friendly reaction. The synthesized compounds are potential biologically active substances and can also be used as «building-blocks» for organic synthesis.

**Keywords:** rearrangement, Vilsmeier-Haack reagent, Michael reaction, catalyst-free and atom-economic reaction.

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***Introduction***

The direct functionalization of the C($sp^3$)−H bond has a significant effect on stimulating the interest of synthetic chemists in such reactions [1−4]. This is because C ($sp^3$)−H bonds are very common in organic compounds. They are one of the least reactive bonds, and their direct functionalization allows skipping the stages of pre-activation, such as halogenation and stoichiometric metallization of the starting substrates. In particular, the direct bonds of the C ($sp^3$)−H center with a heteroatom such as nitrogen, oxygen, and sulfur have been widely studied [5].

Metal-photoredox-catalysis was a breakthrough in the construction of C−C bonds, for example, the combination of nickel catalyst and photoorganocatalyst (benzaldehyde) for C ($sp^3$)−H alkylation/arylation of ethers [6], C($sp^3$)−H arylation of saturated hydrocarbons using nickel salts and diaryl ketones of the photooxidation catalyst [7].

Other strategies for activating C($sp^3$)−H bonds of heterocycles include the use of metal-free catalysts. Despite impressive achievements, studies of synthetic methods for C($sp^3$)−H activation without the use of metals as catalysts are actively developing.

Developing effective approaches to the synthesis of bioactive molecules, we studied the reaction of hydroacridines with Michael acceptors, such as maleimides.

***Results and discussion***

Our previous studies have shown the powerful potential of heterocycles with the heminal arrangement of heteroatoms [8,9]. In particular, the functionalization of N-arylmaleimides by the $sp^3$ carbon atom of hydroacridines under non-catalytic conditions was performed for the first time [10−12].

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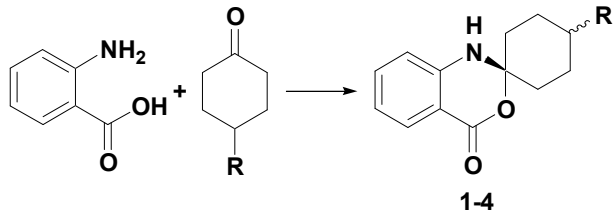
Some of the compounds synthesized in previous studies are potential acetyl- and butylcholinesterase inhibitors or anti-inflammatory agents [13]. Given the strong synthetic and practical potential of compounds of this class, the study of the functionalization of the $sp^3$ carbon atom of hydroacridines was continued. The reaction between hydroacridines and maleimides without a catalyst was made possible by imine-enaminetautomerism in these compounds. The formation of a nucleophilicenamine center on the C-4 carbon atom can explain the relatively easy addition of arylmaleimides by the Michael reaction.

The rearrangement of 3,1-benzoxazines to hydroacridines under the action of Vilsmeier-Haack reagent is already a classic example of electrophilic recycling of hemialdiheteroatomic systems. It was of interest to expand the examples of this rearrangement by replacing phosphorus chloride in the classical Vilsmeier-Haack reagent with phosphorus tribromide, which will allow introducing bromine atom into the pyridine cycle.

For the synthesis of new derivatives of 3,1-benzoxazines 1–4, the literature method was used [14], the interaction of anthranilic acid with cyclic ketones in toluene without a catalyst with azeotropic distillation of water (Scheme 1). Compounds 2–4 are formed as a mixture of diastereomers.




1 R=H (70%); 2 R=Me (75%); 3 R=$C(Me)_3$ (83%); 4 R=$C(Me)_2CH_2Me$ (75%)

Scheme 1

When compounds 1–4 react with a three-fold excess of Vilsmeier-Haack reagent for 1 h, 5–8 chlorochridines are formed, and with a 3-fold excess of modified reagent ($PBr_3$/DMF) for 0.5 h, they regroup to substituted acridones 13–15 at room temperature. Increasing the amount of formulation agent to 6 times and the molar excess and the reaction time to 1 h leads to the formation of bromoacridines 9–12 (Scheme 2).

The structure of all synthesized compounds is established with the help of modern physicochemical research methods.

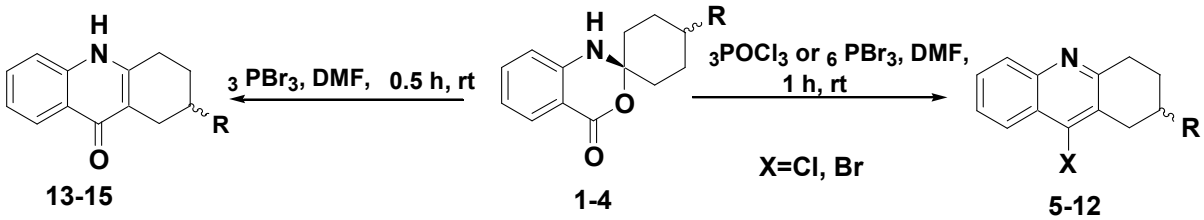
In the interaction of hydroacridines 5–12 with N-arylmaleimides, adducts of Michael 16–27 with moderate yields are formed. The reaction was carried out under non-catalytic conditions by heating the substrates in DMSO at 100–120$^0$C for 4 h. It was found that the reaction is general in nature, easy to proceed, and the isolation of products is not difficult.

There are two chiral centers in the structure of molecules 21 and 22, which means that the formation of four stereoisomers is theoretically possible. However, the absence of duplication of signals in the NMR spectra suggests that only a mirror pair of diastereomers in the ratio 1:1 (*S,R/R,S*) is formed in these reactions. This conclusion is made based on the analysis of data of X-ray structural research of the previous research [11]. All other compounds have three chiral centers and the formation of 8 stereoisomers is possible, but no additional studies have been performed to determine the exact number of isomers formed in this reaction, as well as their relative configuration.

Despite the fact that spectral methods of analysis fail to record the tautomerism of hydroacridines 5–12, the reactions of addition of maleimides to these compounds convincingly prove its existence.

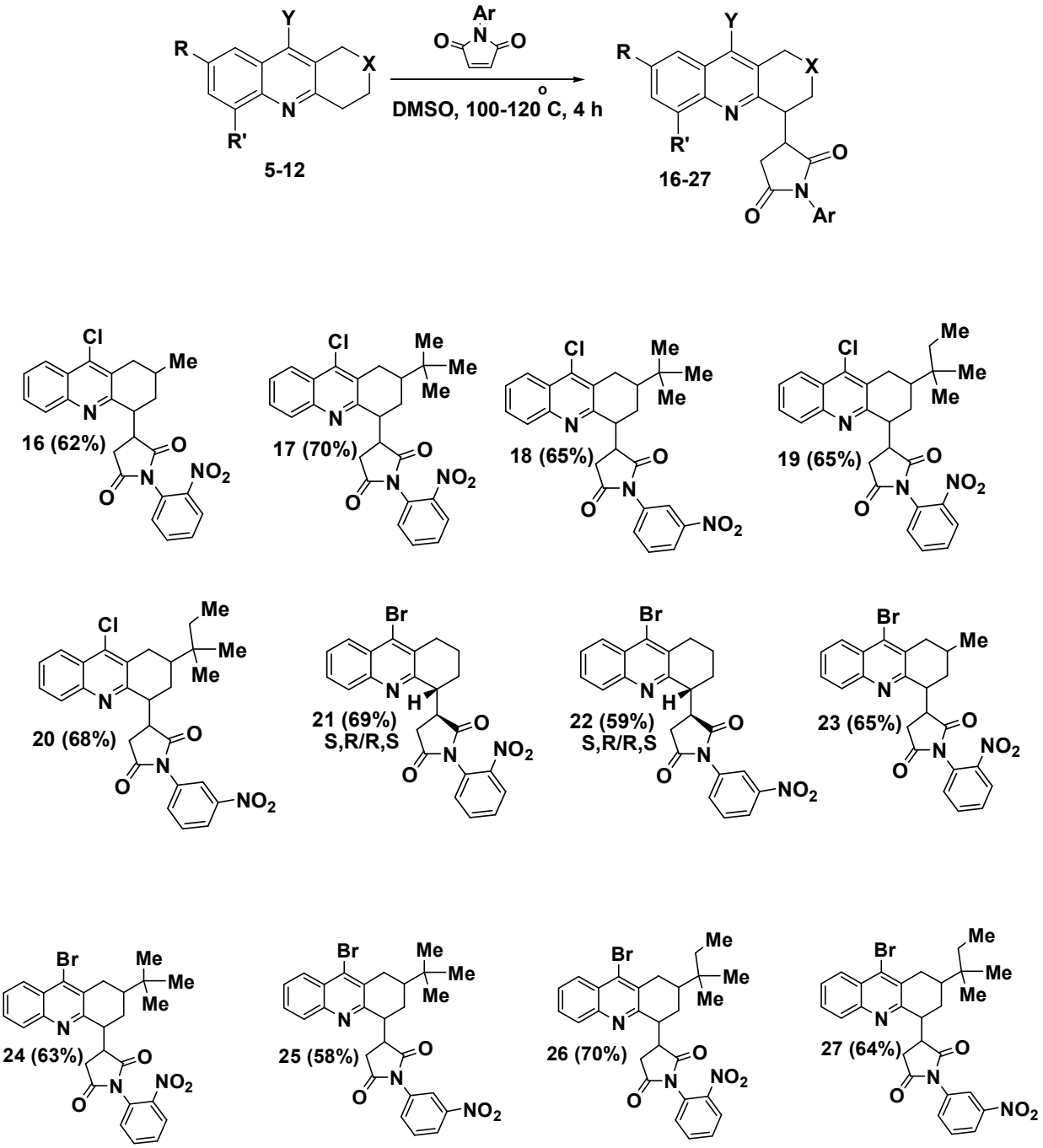
***Conclusions***

The interaction of 3,1-spirobenzoxazines with Vilsmeier-Haack reagent ($POCl_3$($PBr_3$)/DMF),




5 X=Cl, R=H (100%); 6 X=Cl, R=Me (75%); 7X=Cl, R=$C(Me)_3$ (87%); 8 X=Cl, R=$C(Me)_2CH_2Me$ (68%); 9 X=Br,R=H (60%);10 X=Br,R=Me (68%); 11 X=Br,R=$C(Me)_3$ (60%); 12X=Br,R=$C(Me)_2CH_2Me$ (55%); 13 R=H (84%); 14 R=Me (84%); 15 R=$C(Me)_2CH_2Me$ (80%)

Scheme 2




Scheme 3

depending on the amount of formulation agent, leads to the formation of acridones or acridines. The corresponding adducts of Michael were synthesized by the reaction of chloro(bromo)hydroacridines with N-arylmaleimides. The reaction proceeds along the $sp^3$ hybrid carbon atom under non-catalytic conditions due to the imin-enaminetautomerism of chloro-(bromo)hydroacridines. The synthesized compounds are potential biologically active substances.

***Experimental section***

The $^1H$ NMR spectra were obtained by using aBrukerAvance II 400 instrument (400.13 MHz) in DMSO-$d_6$ with $Me_4Si$ as internal standard. The mass

spectra were recorded by means of a MX1321 instrument with direct injection of the sample at an ionization chamber temperature of 200°C and with 70 e Vionizing electrons. The FAB spectra of compounds were recorded by a VG7070 spectrometer. Desorption of the ions from the solution of the samples in metanitrobenzyl alcohol was realized with a beam of argon atoms with energy 8 keV. Elemental analysis was performed by means of a LECOCHNS-900 instrument. The reactions and the purity of the obtained compounds were monitored by TLC on Merck Silicagel 60 F-254 plates with 10:1 $CHCl_3$–i-PrOH as eluent. Melting points were carried out using an Electrothermal 9100 Digital Melting Point apparatus and were uncorrected.Compounds 1, 2, 6, 9, 10, 14 [13] and 13 [15] were obtained by literature methods.

*General methods of synthesis of compounds 1–4*

0.02 mol solution of the corresponding anthranilic acid in 50 ml of toluene is placed in a flask equipped with a Dina-Stark nozzle and 0.022 mol of the corresponding ketone is added. The mixture is boiled for 2 hours. After draining from the nozzle 35 ml of solvent, the residue is poured into a beaker. After cooling to room temperature, a light gray precipitate precipitates from the solution, which is filtered off and washed with a small amount of toluene and hexane. Dried in air to constant weight.

*4'-tert-Butylspiro[3,1-benzoxazine-2,1'-cyclohexane]-4(1H)-one (3)*

Yield 83%, Mp162–167°C. $^1$H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 0.86–0.88 (9H, m, $3CH_3$), 1.04–1.20 (2H, m, $CH_2$), 1.40–1.77 (5H, m, cyclohexane $CH_2$), 2.26–2.29 (1H, m, $CH_2$), 2.41–2.44 (1H, m, $CH_2$), 6.65–6.69 (1H, m, H-Ar), 6.79–6.93 (1H, m, H-Ar), 7.25 (1H, s, NH), 7.35–7.42 (1H, m, H-Ar), 7.89–7.94 (1H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 273 $[M]^+$ (11). Calculated $C_{17}H_{23}NO_2$: C 74.69; H 8.48; N 5.12. Found: C 74.78; H 8.43; N 5.18.

*4'-tert-Amylspiro[3,1-benzoxazine-2,1'-cyclohexane]-4(1H)-one (4)*

Yield 75%, Mp113–118°C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 7.64–7.66 (1H, m, H-Ar), 7,38(1H, s, H-Ar), 7.27 (1H, s, NH), 6.72–6.74 (2H, m, H-Ar), 2.21–2.24 (2H, m, $CH_2$), 1.14–1.57 (9H, m, cyclohexane), 0.75–0.78 (9H, m, $3CH_3$). MS (EI), *m/z* ($I_{rel}$, %): 287 $[M]^+$ (15). Calculated $C_{14}H_{17}NO_2$: C 75.22; H 8.77; N 4.87. Found: C 75.32; H 8.72; N 4.63.

*General method of synthesis of compounds 5–12*

Mix 0.01 mol of the corresponding oxazine with 1 ml of DMF. Vilsmeier-Haack reagent prepared from 6 ml of DMF and 2.75 ml (0.03 mol) of $POCl_3$ was added portion-wise to the suspension under ice-cooling. After 10–15 min, a yellow precipitate begins to fall out of the reaction mass. The reaction is complete after 1 hour. The reaction mixture was poured onto ice and neutralized with concentrated ammonia solution and the precipitate was filtered off.

*2-tert-Butyl-9-chloro-1,2,3,4-tetrahydroacridine (7)*

Yield: 87%. Mp85–87°C.$^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.09 (1H, д, $^3J$=8.3 Hz, H-Ar), 7.92 (1H, d, $^3J$=8.3 Hz, H-Ar), 7.73 (1H, t, $^3J$=7.3 Hz, H-Ar), 7.62 (1H, t, $^3J$=7.3 Hz, H-Ar), 3.06–3.14 (2H, m, $CH_2$), 2.91–3.00 (1H, m, $CH_2$), 2.54–2.57 (1H, m, $CH_2$), 2.04–2.06 (1H, m, CH), 1.52–1.57 (1H, m, $CH_2$), 1.37–1.43 (1H, m, $CH_2$), 0.94–0.98 (9H, m, $3CH_3$).MS (EI), *m/z* ($I_{rel}$, %): 275 $[M(^{37}Cl)]^+$ (24), 273 $[M(^{35}Cl)]^+$ (72). Calculated $C_{17}H_{20}ClN$: C 74.57; H 7.36; N 5.12, Found: C 74.62; H 7.31; N 5.06.

*9-Chloro-2-(1,1-dimethylpropyl)-1,2,3,4-tetrahydroacridine (8)*

Yield: 68%. Mp90–91°C.$^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.11 (1H, d, $^3J$=8.3 Hz, H-Ar), 7.93 (1H, d, $^3J$=8.8 Hz, H-Ar), 7.73 (1H, t, $^3J$=7.3 Hz, H-Ar), 7.63 (1H, t, $^3J$=7.8 Hz, H-Ar), 2.94–3.16 (4H, m, $2CH_2$), 2.59–2.62 (1H, m, $CH_2$), 2.00–2.03 (1H, m, CH), 1.54–1.56 (1H, m, $CH_2$), 1.21–1.28 (2H, m, $CH_2$), 0.76–0.79 (9H, m, $3CH_3$).MS (EI), *m/z* ($I_{rel}$, %): 289 $[M(^{37}Cl)]^+$ (16), 287 $[M(^{35}Cl)]^+$ (45). Calculated $C_{18}H_{22}ClN$: C 75.11; H 7.70; N 4.87, Found: C 75.18; H 7.63; N 4.75.

*2-tert-Butyl-9-bromo-1,2,3,4-tetrahydroacridine (11)*

Yield: 60%. Mp89–91°C.$^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.05 (1H, d, $^3J$=7.8 Hz, H-Ar), 7.89 (1H, d, $^3J$=8.3 Hz, H-Ar), 7.70 (1H, t, $^3J$=7.3 Hz, H-Ar), 7.60 (1H, t, $^3J$=7.8 Hz, H-Ar), 3.01–3.11 (2H, m, $CH_2$), 2.90–2.99 (1H, m, $CH_2$), 2.66–2.71 (1H, m, $CH_2$), 1.99–2.02 (1H, m, CH), 1.49–1.55 (1H, m, $CH_2$), 1.32–1.41 (1H, m, $CH_2$), 0.94–0.96 (9H, m, $3CH_3$).MS (EI), *m/z* ($I_{rel}$, %): 319 $[M(^{81}Br)]^+$ (70), 317 $[M(^{79}Br)+H]^+$ (72). Calculated $C_{17}H_{20}BrN$: C 64.16; H 6.33; N 4.40, Found: C 64.26; H 6.27; N 4.49.

*9-Bromo-2-(1,1-dimethylpropyl)-1,2,3,4-tetrahydroacridine (12)*

Yield: 55%. Mp95–97°C.$^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.04 (1H, d, $^3J$=8.3 Hz, H-Ar), 7.88 (1H, d, $^3J$=8.3 Hz, H-Ar), 7.69 (1H, t, $^3J$=7.3 Hz, H-Ar), 7.59 (1H, t, $^3J$=7.8 Hz, H-Ar), 2.94–3.10 (4H, m, $2CH_2$), 1.93–1.96 (1H, m, CH), 1.58–1.63 (1H, m, $CH_2$), 1.31–1.37 (2H,

m, $CH_2$), 1.19−1.21 (1H, m, $CH_2$), 0.74−0.83 (9H, m, $3CH_3$).MS (FAB), *m/z* ($I_{rel}$, %): 333 [M($^{81}$Br)+H]$^+$ (100), 331 [M($^{79}$Br)+H]$^+$ (100). Calculated $C_{18}H_{22}BrN$: C 65.06; H 6.67; N 4.22. Found: C 65.16; H 6.72; N 4.16.

*2-(1,1-Dimethylpropyl)-1,3,4,10-tetrahydroacridin-9(2H)-one (15)*

When cooled with ice, 2.9 ml of $PBr_3$ (0.03 mol) was added to 4.6 ml of DMF (0.06 mol). The resulting Vilsmeier-Haack reagent was dissolved in 15 ml of chloroform, then 2.87 g of compound 4 (0.01 mol) was added and the mixture was left at room temperature. After 0.5 h, the reaction mixture was poured onto ice and treated with aqueous ammonia solution. The precipitate formed is filtered off. Yield: 80%. Mp365−368$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 11.36 (1H, s, NH), 8.04 (1H, d, $^3J$=7.8 Hz, H-Ar), 7.54 (1H, t, $^3J$=7.3 Hz, H-Ar), 7.44 (1H, d, $^3J$=8.3 Hz, H-Ar), 7.20 (1H, t, $^3J$=7.3 Hz, H-Ar), 2.74−2.75 (2H, m, $CH_2$), 2.63−2.67 (1H, m, $CH_2$), 2.15−2.19 (1H, m, $CH_2$), 1.96−2.01 (1H, m, CH), 1.90−1.93 (2H, m, $CH_2$), 1.33−1.38 (2H, m, $CH_2$), 0.82−0.86 (9H, m, $3CH_3$).MS (EI), *m/z* ($I_{rel}$, %): 269 [M]$^+$ (10). Calculated $C_{18}H_{23}NO$: C 80.26; H 8.61; N 5.20. Found: C 80.38; H 8.55; N 5.26.

*General method of synthesis of compounds 16−27*

The corresponding hydroacridines (5 mmol) and the corresponding N-arylmaleimide (5 mmol) were dissolved in 3 ml of DMSO. The mixture was heated at 100−120$^0$C for 4 h. After cooling to room temperature, 20 ml of water was added. The precipitate formed was filtered off and recrystallized from DMF.

*3-(9-Chloro-2-methyl-1,2,3,4-tetrahydroacridin-4-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (16)*

Yield 58%, Mp205−208$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.15−1.16 (3H, m, $CH_3$), 1.50−1.57 (1H, m, CH), 1.89−2.11 (4H, m, $2CH_2$), 2.97−3.01 (2H, m, $CH_2$), 3.57−3.72 (1H, m, CH) , 3.82−3.90 (1H, m, CH), 7.63−7.77 (5H, m, H-Ar), 7.74 (1H, s, H-Ar), 8.13−8.21 (2H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 451 [M($^{37}$Cl)]$^+$ (8), 449 [M($^{35}$Cl)]$^+$ (22). Calculated $C_{24}H_{20}ClN_3O_4$: C 64.07; H 4.48; N 9.34. Found: C 64.25; H 4.37; N 9.17.

*3-(2-tert-Butyl-9-chloro-1,2,3,4-tetrahydroacridin-4-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (17)*

Yield 62%, Mp170−173$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.00 (9H, c, $3CH_3$), 1.55−1.58 (1H, м, CH), 1.72−2.00 (4H, м, $2CH_2$), 2.67−2.73 (2H, м, $CH_2$), 3.10−3.14 (1H, м, CH) , 3.62−3.76 (1H, м, CH), 7.66−7.74 (5H, м, H-Ar), 7.95 (1H, c, H-Ar), 8.10−8.14 (2H, м, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 493 [M($^{37}$Cl)]$^+$ (5), 491 [M($^{35}$Cl)]$^+$ (12). Calculated $C_{27}H_{26}ClN_3O_4$: C 65.92; H 5.33; N 8.54. Found: C 65.83; H 5.39; N 8.69.

*3-(2-tert-Butyl-9-chloro-1,2,3,4-tetrahydroacridin-4-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (18)*

Yield 75%, Mp240−242$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.02 (9H, m, $3CH_3$), 1.47−1.50 (1H, m, CH), 2.05−2.29 (4H, m, $2CH_2$), 2.72−2.79 (2H, m, $CH_2$), 3.12−3.16 (1H, m, CH) , 3.77−3.93 (1H, m, CH), 7.46−7.49 (1H, m, H-Ar), 7.58−7.60 (1H, m, H-Ar), 7.64−7.72 (2H, m, H-Ar), 7.87−7.95 (2H, m, H-Ar), 8.00−8.02 (1H, s, H-Ar), 8.13−8.16 (1H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 493 [M($^{37}$Cl)]$^+$ (6), 491 [M($^{35}$Cl)]$^+$ (14). Calculated $C_{27}H_{26}ClN_3O_4$: C 65.92; H 5.33; N 8.54. Found: C 65.88; H 5.45; N 8.48.

*3-[9-Chloro-2-(1,1-dimethylpropyl)-1,2,3,4-tetrahydroacridin-4-yl]-1-(2-nitrophenyl)pyrrolidine-2,5-dione (19)*

Yield 62%, Mp250−252$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.14−8.16 (2H, m, H-Ar), 7.94 (1H, s, H-Ar), 7.66−7.81 (5H, m, H-Ar), 3.62−3.70 (1H, m, CH), 3.07−3.11 (1H, m, CH), 2.72−2.88 (2H, m, $CH_2$), 2.15−2.38 (2H, m, $CH_2$), 1.88−1.93 (1H, m, CH), 1.22−1.41 (4H, m, $CH_2$), 0.79−0.93 (9H, m, $3CH_3$). MS (EI), *m/z* ($I_{rel}$, %): 507 [M($^{37}$Cl)]$^+$ (25), 505 [M($^{35}$Cl)]$^+$ (100). Calculated $C_{28}H_{28}ClN_3O_4$: C 66.46; H 5.58; N 8.30. Found: C 66.56; H 5.54; N 8.39.

*3-[9-Chloro-2-(1,1-dimethylpropyl)-1,2,3,4-tetrahydroacridin-4-yl]-1-(3-nitrophenyl)pyrrolidine-2,5-dione (20)*

Yield 70%, Mp265−267$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.14−8.28 (2H, m, H-Ar), 7.95 (1H, s, H-Ar), 7.67−7.89 (5H, m, H-Ar), 3.53−3.65 (1H, m, CH), 3.05−3.13 (1H, m, CH), 2.73−2.88 (2H, m, $CH_2$), 2.12−2.36 (2H, m, $CH_2$), 1.86−1.92 (1H, m, CH), 1.24−1.42 (4H, m, $CH_2$), 0.79−0.95 (9H, m, $3CH_3$). MS (EI), *m/z* ($I_{rel}$, %): 507 [M($^{37}$Cl)+H]$^+$ (36), 505 [M($^{35}$Cl)+H]$^+$ (100). Calculated $C_{28}H_{28}ClN_3O_4$: C 66.46; H 5.58; N 8.30. Found: C 66.54; H 5.51; N 8.22.

*3-(9-Bromo-1,2,3,4-tetrahydroacridin-4-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (21)*

Yield 65%, Mp190−192$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.69−1.72 (2H, m, $CH_2$), 2.08−2.18 (4H, m, $2CH_2$), 2.72−2.88 (2H, m, $CH_2$), 3.08−3.12 (1H, m, CH) , 3.84−3.88 (1H, m, CH), 7.65−7.78 (5H, m, H-Ar), 8.10−8.11 (1H, m, H-Ar), 8.20−8.22 (2H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 481 [M ($^{81}$Br)]$^+$ (24), 479 [M ($^{79}$Br)]$^+$ (20). Calculated $C_{23}H_{18}BrN_3O_4$: C 57.51; H 3.78; N 8.75. Found: C 57.45; H 3.85; N 8.62.

*3-(9-Bromo-1,2,3,4-tetrahydroacridin-4-yl)-1-*

*(3-nitrophenyl)pyrrolidine-2,5-dione (22)*

Yield 65%, Mp185–186$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.71–1.75 (2H, m, $CH_2$), 2.09–2.27 (4H, m, $2CH_2$), 2.72–2.87 (2H, m, $CH_2$), 3.08–3.12 (1H, m, CH) , 3.87–3.92 (1H, m, CH), 7.65–7.81 (5H, m, H-Ar), 7.92–7.94 (1H, m, H-Ar), 8.27–8.32 (2H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 481 [M ($^{81}$Br)]$^+$ (20), 479 [M ($^{79}$Br)]$^+$ (24). Calculated $C_{23}H_{18}BrN_3O_4$: C 57.51; H 3.78; N 8.75. Found: C 57.55; H 3.87; N 8.65.

*3-(9-Bromo-2-methyl-1,2,3,4-tetrahydroacridin-4-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (23)*

Yield 68%, Mp206–207$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.15–1.16 (3H, m, $CH_3$), 1.51–1.66 (1H, m, CH), 1.86–2.09 (4H, m, $2CH_2$), 2.97–3.01 (2H, m, $CH_2$), 3.56–3.73 (1H, m, CH) , 3.85–3.89 (1H, m, CH), 7.65–7.75 (5H, m, H-Ar), 7.94 (1H, s, H-Ar), 8.10–8.17 (2H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 495 [M ($^{81}$Br)]$^+$ (16), 493 [M ($^{79}$Br)]$^+$ (15). Calculated $C_{24}H_{20}BrN_3O_4$: C 58.31; H 4.08; N 8.50. Found: C 58.23; H 4.13; N 8.47.

*3-(9-Bromo-2-tert-butyl-1,2,3,4-tetrahydroacridin-4-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (24)*

Yield 69%, Mp175–177$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.00 (9H, s, $3CH_3$), 1.56–1.59 (1H, m, CH), 1.74–1.98 (4H, m, $2CH_2$), 2.65–2.73 (2H, m, $CH_2$), 3.11–3.13 (1H, m, CH) , 3.76–3.79 (1H, m, CH), 7.69–7.75 (5H, m, H-Ar), 7.95 (1H, s, H-Ar), 8.11–8.16 (2H, m, H-Ar). MS (EI), *m/z* ($I_{rel}$, %): 537 [M ($^{81}$Br)]$^+$ (8), 535 [M ($^{79}$Br)]$^+$ (8). Calculated $C_{27}H_{26}BrN_3O_4$: C 60.45; H 4.89; N 7.83. Found: C 60.55; H 4.76; N 7.82.

*3-(9-Bromo-2-tert-butyl-1,2,3,4-tetrahydroacridin-4-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (25)*

Yield 59%, Mp240–241$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 1.03 (9H, m, $3CH_3$), 1.48–1.51 (1H, m, CH), 2.07–2.32 (4H, m, $2CH_2$), 2.73–2.89 (2H, m, $CH_2$), 3.14–3.18 (1H, m, CH) , 3.79–3.92 (1H, m, CH), 7.46–7.48 (1H, m, H-Ar), 7.57–7.59 (1H, m, H-Ar), 7.66–7.71 (2H, m, H-Ar), 7.89–7.95 (2H, m, H-Ar), 8.01–8.03 (1H, s, H-Ar), 8.11–8.13 (1H, m, H-Ar).MS (EI), *m/z* ($I_{rel}$, %): 537 [M ($^{81}$Br)]$^+$ (8), 535 [M ($^{79}$Br)]$^+$ (15). Calculated $C_{27}H_{26}BrN_3O_4$: C 60.45; H 4.89; N 7.83. Found: C 60.39; H 4.79; N 7.75.

*3-[9-Bromo-2-(1,1-dimethylpropyl)-1,2,3,4-tetrahydroacridin-4-yl]-1-(2-nitrophenyl)pyrrolidine-2,5-dione (26)*

Yield 65%, Mp232–234$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.12–8.14 (2H, m, H-Ar), 7.90 (1H, s, H-Ar), 7.61–7.77 (5H, m, H-Ar), 3.60–3.63 (1H, m, CH), 3.07–3.19 (1H, m, CH), 2.74–2.86 (2H, m, $CH_2$), 2.11–2.30 (2H, m, $CH_2$), 1.80–1.91 (1H, m, CH), 1.24–1.39 (4H, m, $CH_2$), 0.79–0.93 (9H, m, $3CH_3$). MS (FAB), *m/z* ($I_{rel}$, %): 550 [M($^{79}$Br)+H]$^+$ (25), 552 [M($^{81}$Br)+H]$^+$ (100). Calculated $C_{28}H_{28}BrN_3O_4$: C 61.10; H 5.13; N 7.63. Found: C 61.56; H 5.54; N 7.39.

*3-[9-Bromo-2-(1,1-dimethylpropyl)-1,2,3,4-tetrahydroacridin-4-yl]-1-(3-nitrophenyl)pyrrolidine-2,5-dione (27)*

Yield 63%, Mp252–254$^0$C. $^1$H NMR spectrum (400 MHz, DMSO-$d_6$), δ, ppm: 8.14–8.28 (2H, m, H-Ar), 7.95 (1H, s, H-Ar), 7.67–7.89 (5H, m, H-Ar), 3.53–3.65 (1H, m, CH), 3.05–3.13 (1H, m, CH), 2.73–2.88 (2H, m, $CH_2$), 2.12–2.36 (2H, m, $CH_2$), 1.86–1.92 (1H, m, CH), 1.24–1.42 (4H, m, $CH_2$), 0.79–0.95 (9H, m, $3CH_3$). MS (FAB), *m/z* ($I_{rel}$, %): 550 [M($^{79}$Br)+H]$^+$ (25), 552 [M($^{81}$Br)+H]$^+$ (100). Calculated $C_{28}H_{28}BrN_3O_4$: C 61.10; H 5.13; N 7.63. Found: C 61.47; H 5.36; N 7.22.

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## АТОМ-ЕКОНОМНА РЕАКЦІЯ МІХАЕЛЯ МІЖ ГІДРОАКРИДИНАМИ ТА АРИЛМАЛЕЇМІДАМИ БЕЗ ДОДАВАННЯ КАТАЛІЗАТОРА

***М.В. Сметанін, С.А. Варениченко, О.В. Мазепа, О.К. Фарат, О.В. Харченко, В.І. Марков***

Реакцією антранілової кислоти з циклічними кетонами було синтезовано раніше невідомі спіропохідні 3,1-бензоксазинів. Взаємодія 3,1-спіробензоксазинів з реактивом Вільсмайєра-Хаака ($POCl_3$($PBr_3$)/DMF), залежно від кількості агента в методиці, приводить до утворення гідроакридонів або гідроакридинів. В умовах без додавання каталізаторів N-арилмалеіміди, як і акцептори Міхаеля, реагують з гідроакридинами у ДМСО з утворенням відповідних аддуктів. Реакція протікає стереоселективно з утворенням дзеркальної пари діастереомерів, якщо продукти мають лише два хіральних центри. За наявності в структурі аддуктів Міхаеля трьох хіральних центрів реакція не є стереоселективною. Реакція протікає за допомогою $sp^3$ гібридизованого атома вуглецю в некаталітичних умовах завдяки імін-енаміновій таутомерії хлор(бром)гідроакридинів. Дану реакцію також можна розглядати як ефективну атом-економну аза-енову реакцію, яка повністю відповідає сучасним вимогам до екологічної реакції. Синтезовані сполуки є потенційними біологічно активними речовинами, а також можуть бути використані як «будівельні блоки» для органічного синтезу.

**Ключові слова**: перегрупування, реагент Вільсмайєра-Хаака, реакція Міхаеля, безкаталізаторна та атом-економна реакція.

## ATOM-ECONOMIC MICHAEL REACTION BETWEEN HYDROACRIDINES AND ARYLMALEIMIDES WITHOUT CATALYST/ADDITIVE

***N.V. Smetanin [a], S.A. Varenichenko [a,*], A.V. Mazepa [b], O.K. Farat [a], A.V. Kharchenko [a], V.I. Markov [a]***

**[a] Ukrainian State University of Chemical Technology, Dnipro, Ukraine**

**[b] A.V. Bogatsky Physico-Chemical Institute of the National Academy of Sciences of Ukraine, Odessa, Ukraine**

**[*] e-mail: svetlanavarenichenko@gmail.com**

Previously unknown spiroderivatives of 3,1-benzoxazines were synthesized by the reaction of anthranilic acid with cyclic ketones. The interaction of 3,1-spirobenzoxazines with Vilsmeier-Haack reagent ($POCl_3$ ($PBr_3$)/DMF), depending on the amount of formulation agent, leads to the formation of hydroacridones or hydroacridines. Under catalyst- and additive-free conditions, N-arylmaleimides, like Michael's acceptors, are added to the hydroacridines in DMSO to form the corresponding adducts. The reaction proceeds stereoselectively with the formation of a mirror pair of diastereomers, if the products have only two chiral centers.In the presence of three chiral centers in the structure of Michael's adducts, the reaction is not stereoselective. The reaction proceeds by the $sp^3$ hybrid carbon atom under non-catalytic conditions due to the imin-enaminetautomerism of chloro(bromo)hydroacridines. The presented reaction can also be considered as an effective atom-economical aza-ene reaction, which fully meets today's requirements for eco-friendly reaction. The synthesized compounds are potential biologically active substances and can also be used as «building-blocks» for organic synthesis.

**Keywords:** rearrangement; Vilsmeier-Haack reagent; Michael reaction; catalyst-free and atom-economic reaction.

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