UDC547.835+547.831

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

FUNCTIONALIZATION OF N-ARYLMALEIMIDES BY sp^3 C−H BONDS OF HYDROACRIDINES(QINOLINES)

[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

The catalyst-free sp^3 C−H functionalization of tetrahydroacridine(quinolines) derivatives has been achieved using a Michael-type reaction with N-arylmaleimides. This method enables the facile synthesis of biologically important N-aryl bearing tetrahydroacridine(quinolines) moieties in a single step with high yields. The reaction occurs under non-catalytic conditions by heating of hydroacridines(quinolines) in DMSO within 4 h at 100−120°C. The reaction between starting compounds allows synthesizing (3S/4R)-3-[(3R/4S)-9-chloroacridine(quinoline)-4-yl]-1(-N-aryl)pyrrolidine-2,5-diones with a good yield. The structure of compounds was proved by spectral methods of analysis. The ^{1}H NMR spectrum shows characteristic signals of protons of the CH-groups in acridine(quinoline) (3.4−3.5 ppm) and pyrrolidine (3.8−3.9 ppm) cycles.It is interesting to note that the main direction of the fragmentation is the Michael retro-reaction, which is accompanied by the elimination of 1-(2-nitrophenyl)-1H-pyrrole-2,5-dione and leads to the formation of m/z ions of starting chloroacridines(quinolines).

Keywords: benzylic sp^3 C−H activation, catalyst free, Michael reaction, N-arylmaleimides, hydroacridine(quinoline) derivatives.

DOI: 10.32434/0321-4095-2020-133-6-165-170

Introduction

The benzylic sp^3 C−H bond functionalization of 2-alkylazaarenes has been thoroughly studied. Usually, these reactions are catalyzed by transition metals, such as scandium [1], copper [2], palladium [3], iron [4], ytterbium [5], or by Brønsted acids [6]. Numerous publications in this field emphasized the practical value of compounds of this class. Nowadays, the functionalization of related compounds has been achieved without the use of metal catalysts [7,8]. During the development of effective approaches to the synthesis of bioactive molecules, we studied the reaction of hydroacridines with Michael acceptors, such as maleimides and acrylonitrile [9,10]. For the first time, hydroacridines were functionalized with Michael acceptors, such as N-arylmaleimides. The reaction takes place under non-catalytic conditions by heating hydroacridines in DMSO within 4 h at the temperature of 100−120°C with good yields. Due to the presence of two chiral centers, the formation of four stereoisomers is theoretically possible in the reaction. However, the absence of signal doubling in the NMR spectra suggests that only a mirror pair of diastereomers is formed in a ratio of 1:1 (S,R/R,S), and proved by X-ray analysis [9]. Given both the practical value of hydroacridines and the new method of direct conversion of the sp^3-CH bond of these compounds, the number of examples of effective functionalization has been expanded.

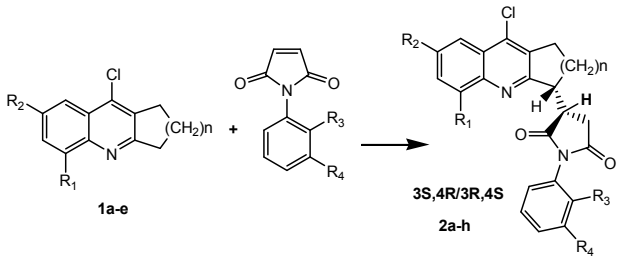
Results and discussion

The starting chloroacridine1a was obtained by rearrangement the spiro derivative of 3,1-benzoxazine under the action of formylation agent in quantitative yield [11]. Chloroacridines 1b,c [12,13] and chloro-quinoline 1d [14] were synthesized by the methods described in literature. The reaction between starting compounds 1a-d allows synthesizing (3S/4R)-3-[(3R/4S)-9-chloroacridine(quinoline)-4-yl]-1(-N-aryl)-pyrrolidine-2,5-diones 2a-f with a good yield (Scheme 1). The structure of compounds 2a−f was proved by spectral methods of analysis. The ^{1}H NMR spectrum is characterized by proton signals of the

CH groups of the acridine (3.4–3.5 ppm) and pyrrolidine (3.8–3.9 ppm) cycles. Product yields are presented in Table.

The yields of compounds 2a–f

Compound	n	R_1	R_2	R_3	R_4	Yield, %
2a	2	H	Br	NO_2	H	90
2b	2	H	Br	H	NO_2	94
2c	2	H	CH_3	NO_2	H	53
2d	2	CH_3	H	NO_2	H	49
2e	3	H	H	NO_2	H	76
2f	3	H	H	H	NO_2	89

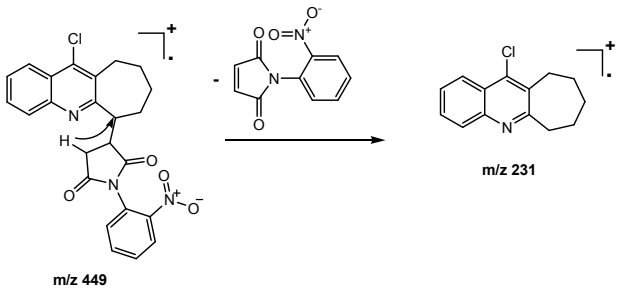


1: a) n=2, R_1=H, R_2=Br;b) n=2, R_1=H, R_2=CH_3; c)n=2, R_1=CH_3, R_2=H;d) n=3, R_1=H, R_2=H

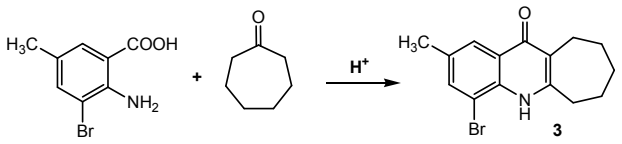
Scheme 1

The mass spectrum (EI) of compound 2e contains a peak molecular ion m/z 449 (34%). Two minor primary processes of their decay are accompanied by the elimination of a hydroxyl radical (probably with the participation of an oxygen atom of one of the carbonyl groups) and a chlorine atom, which leads to the formation of pair of electron ions with masses 432 and 414, corresponding to the peaks of average intensity of 10% and 24%, respectively. It is interesting to note that the main direction of the fragmentation is the Michael retro-reaction, which is accompanied by the elimination of 1-(2-nitrophenyl)-1H-pyrrole-2,5-dione and leads to the formation of m/z ions 231. High peak intensity of these fragment ions (100%) is due to a high stability of the conjugate structure of the paired electron neutral particle, which is eliminated (Scheme 2). A similar pattern of fragmentation is observed for other compounds.

Earlier, we developed a convenient method for obtaining chloracridines with quantitative yield by rearrangement of 3,1-benzoxazines under the action of Vilsmeier-Haack reagent [11,15]. Due to direct boiling of anthranilic acid, derivatives with ketones in a large excess of phosphorus chloride requires purification from a large number of by-product resinous products. However, the interaction of 2-amino-3-bromo-5-methylbenzoic acid with cycloheptanone in the catalysis of p-TsOH with azeotropic distillation of water for 3 h produces acridone 3 instead of the expected spiro compound (Scheme 3).



Scheme 2



Scheme 3

Subsequent interaction of acridone 3 with Vilsmeier-Haack reagent leads to the formation of the required chlorquinoline 4 (Scheme 4).

Scheme 4

The presence of a bromine atom in the p-position relative to the nitrogen atom in compounds 1a,b does not interfere with the reaction, while the synthesized chloroquinoline 4 does not react with maleinimides under these conditions. Increasing the reaction time and temperature does not help to carry out the reaction under non-catalytic conditions.

Conclusions

Thus, we have discovered the atom-economical approach to the functionalization of partially hydrogenated acridines(quinolines) based on a simple catalyst-free addition to maleimides.The synthesized compounds are highly functionalized and could serve as low-molecular-weight building blocks for organic synthesis.

Experimental section

The ^{1}H NMR and ^{13}C NMR spectra were obtained by using a BrukerAvance II 400 instrument (400.13 MHz and 100.62 MHz for ^{1}H and ^{13}C, respectively) in DMSO-d_6 or DMSO-d_6/CF_3CO_2D, 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 eV ionizing electrons. The FAB spectra of compounds were recorded by a VG7070 spectrometer. Desorption of the ions from the solution of the samples in *meta*-nitrobenzyl 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. The spectroscopic parameters of compound 1a–dwere described ina previous work.

Synthesis of compounds 2a-f (general method)

Compound 1a–d and corresponding maleimide (5 mmol) were dissolved in 3 mL of DMSO. The mixture was heated at 100–120°C for 4 h. After cooling to room temperature, 20 mL of water was added. The formed precipitate was filtered off and recrystallized from DMF.

3-(7-bromo-9-chloro-1,2,3,4-tetrahydroacridin-4-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (2a)

Light-yellow powder, mp 240–242°C.^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.70–1.72 (2H, m, CH_2), 1.90–1.91 (2H, m, CH_2), 2.08–2.21 (2H, m CH_2), 2.88–3.00 (2H, m, CH_2), 3.60–3.80 (2H, m, CH), 7.46–7.48 (1H, m, H-Ar-NO_2), 7.77–7.75 (2H, m, H-Ar-NO_2), 7.83 (1H, d, ^3J=7.8,Ar), 8.00–8.01 (1H, m, H-Ar-NO_2), 8.1 (1H, d, ^3J=7.8, H-Ar), 8.24 (1H, s, H-Ar).^{13}C NMR (100 MHz, DMSO-d_6/CF_3CO_2D), δ, ppm: 21.7, 21.9, 27.6, 35.6, 41.2, 49.3, 120.2, 125.1, 127.8, 129.3, 130.9, 133.8, 134.9, 138.3, 138.7, 138.9, 139.2, 142.4, 148.5, 156.2, 160.5, 180.5 (CO), 181.5 (CO).MS (EI), *m/z* ($I_{rel,}$ %): 515 [M(^{81}Br)]$^+$ (13), 513 [M(^{79}Br)]$^+$ (8).Calculated for $C_{23}H_{17}BrClN_3O_4$(%): C 53.67; H 3.33; N 8.16, Found (%): C 53.79; H 3.45; N 8.09.

3-(7-bromo-9-chloro-1,2,3,4-tetrahydroacridin-4-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (2b)

Light-yellow powder, mp 232–234°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.60–1.64 (2H, m, CH_2), 1.90–1.94 (2H, m, CH_2), 2.08–2.17 (2H, m, CH_2), 2.88–2.90 (2H, m, CH_2), 3.49–3.50 (1H, m, CH acridine), 3.83–3.85 (1H, m, CH pyrrolidine), 7.38–7.40 (1H, m, H-Ar-NO_2), 7.77–7.78 (1H, m, H-Ar-NO_2), 7.90 (1H, m, H-Ar-NO_2), 7.98 (1H, d, ^3J=8.3 Hz, H-Ar), 8.21 (1H, s, H-Ar-NO_2), 8.33 (1H, d, ^3J=8.3 Hz, H-Ar), 8.37 (1H, s, H-Ar).^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 21.4, 27.1, 27.5, 30.8, 43.2, 43.3, 120.6, 120.8, 122.5, 125.2, 125.8, 130.2, 130.5, 130.9, 132.5, 132.9, 133.8, 139.3, 143.7, 147.8, 159.4, 175.9 (CO), 178.3 (CO). MS (EI), *m/z* ($I_{rel,}$ %): 515 [M (^{81}Br)]$^+$ (19), 513 [M (^{79}Br)]$^+$ (15). Calculated for $C_{23}H_{17}BrClN_3O_4$(%): C 53.67; H 3.33; N 8.16, Found (%): C 53.54; H 3.20; N 8.29.

3-(9-chloro-7-methyl-1,2,3,4-tetrahydroacridin-4-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (2c)

Yellow powder, mp188–190°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.80–1.84 (2H, m, CH_2), 2.09–2.25 (4H, m, $2CH_2$), 2.53 (3H, s, CH_3), 2.88–2.90 (2H, m, CH_2), 3.60–3.62 (1H, m, CH acridine), 3.80–3.82 (1H, m, CH pyrrolidine), 7.50–7.51 (1H, m, H-Ar), 7.58–7.60 (1H, m, H-Ar), 7.70–7.77 (3H, m, H-Ar), 7.89–7.91 (1H, m, H-Ar), 8.14–8.16 (1H, m, H-Ar). MS (FAB), *m/z* ($I_{rel,}$ %):452 [M(^{37}Cl)+H]$^+$ (37), 450 [M(^{35}Cl)+H]$^+$ (100). Calculated for $C_{24}H_{20}ClN_3O_4$(%): C 64.07; H 4.48; N 9.34, Found (%): C 64.19; H 4.29; N 9.59.

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

Yellow powder, mp175–177°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.78–1.81 (2H, m, CH_2), 2.23–2.34 (4H, m, $2CH_2$), 2.52 (3H, s, CH_3), 2.90–2.93 (2H, m, CH_2), 3.44–3.46 (1H, m, CH acridine), 3.81–3.83 (1H, m, CH pyrrolidine), 7.55–7.59 (2H, m, H-Ar), 7.60–7.62 (1H, m, H-Ar), 7.75–7.77 (2H, m, H-Ar), 7.98–8.01 (2H, m, H-Ar).Calculated for $C_{24}H_{20}ClN_3O_4$(%): C 64.07; H 4.48; N 9.34, Found (%): C 64.03; H 4.39; N 9.46.

3-(11-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-6-yl)-1-(2-nitrophenyl)pyrrolidine-2,5-dione (2e):

White powder, mp 205–207°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.26–1.28 (2H, m, CH_2), 1.83–2.09 (4H, m, $2CH_2$), 2.88–2.90 (2H, m, CH_2), 3.55–3.64 (2H, m, CH_2), 3.94–3.96 (1H, m, CH quinolin), 4.10–4.12 (1H, m, CH pyrrolidine), 7.69–7.76 (5H, m, H-Ar), 7.94–7.96 (1H, m, H-Ar), 8.13–8.20 (1H, m, H-Ar).^{13}C NMR (100 MHz, DMSO-d_6), d, ppm: 26.2, 26.3, 29.0, 29.2, 29.8, 30.4, 30.9, 123.9, 124.0, 124.5, 125.4, 125.6, 127.5, 127.6, 128.0, 129.1, 129.6, 129.8, 133.3, 134.3, 134.4, 145.1, 162.8, 175.6 (CO), 177.8 (CO). MS (EI), *m/z* ($I_{rel,}$ %): 451 [M(^{35}Cl)]$^+$ (10), 449 [M(^{35}Cl)]$^+$ (33). Calculated for $C_{24}H_{20}ClN_3O_4$(%): C 64.07; H 4.48; N 9.34, Found (%): C 64.01; H 4.56; N 9.49.

3-(11-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinolin-6-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (2f)

White powder, mp 235–237°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.50–1.57 (2H, m, CH_2), 1.95–2.12 (4H, m, $2CH_2$), 3.06–3.13 (2H, m, CH_2), 3.56–3.58 (2H, m, CH_2), 3.89–3.92 (1H, m, CH quinolin), 4.12–4.14 (1H, m, CH pyrrolidine), 7.48–7.50 (1H, m, H-Ar), 7.67–7.72

(3H, m, H-Ar), 7.78 (1H, t, ^3J=8.3 Hz, H-Ar-NO_2), 8.09 (1H, s, H-Ar-NO_2), 8.14 (1H, d, ^3J=8.3 Hz, H-Ar-NO_2), 8.24 (1H, d, ^3J=8.3 Hz, H-Ar-NO_2).^{13}CNMR (100 MHz, TFA-*d*), δ, ppm: 27.5, 28.6, 31.2, 31.4, 36.6, 44.3, 48.8, 122.9, 124.7, 127.2, 128.9, 129.5, 133.6, 134.2, 134.3, 135.9, 138.3, 138.7, 138.7, 151.2, 155.5, 163.3, 180.6 (CO), 184.2 (CO). MS (EI), *m/z* ($I_{rel,}$ %): 451 [M(^{35}Cl)]$^+$ (9), 449 [M(^{35}Cl)]$^+$ (24). Calculated for $C_{24}H_{20}ClN_3O_4$(%): C 64.07; H 4.48; N 9.34, Found (%): C 64.23; H 4.39; N 9.19.

4-Bromo-2-methyl-5,6,7,8,9,10-hexahydro-11H-cyclohepta[b]quinolin-11-one (3)

A mixture of the 2-amino-3-bromo-5-methylbenzoic acid (0.10 mol), cycloheptanone (0.12 mol) and p-TsOH*H_2O (0.05 mol) in toluene (70 mL) was relfuxed for 6 h with continuous removal of water with a Dean-Stark trap. A solvent was evaporated to dryness under reduced pressure, the solid residue was washed with 5% aq NaOH solution and filtered off. Yield 80%, white powder, mp 298–300^{0}C (DMF). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz):1.44–1.46 (2H, m, CH_2), 1.63–1.65 (2H, m, CH_2), 1.78–1.80 (2H, m, CH_2), 2.38 (3H, s, CH_3), 2.76–2.77 (2H, m, CH_2), 3.02–3.04 (2H, m, CH_2), 7.77 (1H, s, H-Ar), 7.91 (1H, s, H-Ar), 10.02 (1H, br.s., NH). MS (FAB), *m/z* ($I_{rel,}$ %): 308 [M+H (^{81}Br)]$^+$ (90), 306 [M+H (^{79}Br)]$^+$ (100). Calculated for $C_{15}H_{16}BrNO$(%): C 58.84; H 5.27; N 4.57, Found (%): C 58.78; H 5.11; N 4.69.

4-Bromo-11-chloro-2-methyl-7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline (4)

Compound 3 (0.01 mol) was added to DMF (1 mL). The suspension formed was treated with the ice-cold Vilsmeier reagent obtained from DMF (0.09 mol) and $POCl_3$ (0.03 mol) under ice-cooling. A yellow solid precipitated abundantly within 10–15 min. After 0.5 h, the reaction mixture was poured on ice and treated with aq ammonia, the obtained solid was filtered off and dried to give quinoline 4, as yellow powder, yield 90%, mp127–129^{0}C. ^{1}HNMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): ^{1}HNMR (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.67–1.69 (2H, m, CH_2), 1.81–1.82 (2H, m, CH_2), 2.49 (3H, s, CH_3, overlapped with DMSO signals), 3.14–3.16 (2H, m, CH_2), 3.18–3.20 (2H, m, CH_2), 7.86 (1H, s, H-Ar), 7.94 (1H, s, H-Ar). MS (FAB), *m/z* ($I_{rel,}$ %): 326 [M+H (^{81}Br)]$^+$ (90), 324 [M+H (^{79}Br)]$^+$ (100). Calculated for $C_{15}H_{15}BrClN$(%): C 55.49; H 4.66; N 4.31, Found (%): C 55.63; H 4.89; N 4.19.

REFERENCES

1. *Lewis* acid catalyzed benzylic C–H bond functionalization of azaarenes;addition to imines and enones / Komai H., Yoshino T., Matsunaga S., Kanai M. // Synthesis. – 2012.– Vol.44.– No. 14.– P.2185-2194.

2. *C(sp^3)–C(sp^3) bond* formation via copper/Bronsted acid co-catalyzed C(sp^3)–H bond oxidative cross-dehydrogenative-coupling (CDC) of azaarenes / Wang F.-F., Luo C.-P., Deng G., Yang L. // Green Chem. – 2014. – Vol.16.– No. 5.– P.2428-2431.

3. *Metal* catalyzed C(sp^3)–H bond amination of 2-alkyl azaarenes with diethyl azodicarboxylate / Liu J.Y., Niu H.Y., Wu S., Qu G.R., Guo H.M. // Chem. Commun. – 2012.– Vol.48.– No. 78.– P.9723-9725.

4. *Iron catalyzed* synthesis of 2 vinylquinolines via sp^3 C–H functionalization and subsequent C–N cleavage / Li Y., Guo F., Zha Z., Wang Z. // Chem.Asian J. – 2013. – Vol.8.– No. 3.–P.534-537.

5. *Graves, V.B., Shaikh A.* Lewis acid-catalyzed C sp^3–H functionalization of methyl azaarenes with α-trifluoromethyl carbonyl compounds // Tetrahedron Lett. – 2013.– Vol.54.– No. 7.– P.695-698.

6. *Regiospecific* synthesis of gem-dinitro derivatives of 2-halogenocycloalka[b]pyridine-3,4-dicarbonitriles / Ershov O.V., Maksimova V.N., Lipin K.V., Belikov M.Yu., Ievlev M.Yu., Tafeenko V.A., Nasakin O.E.// Tetrahedron. – 2015.– Vol.71.– No. 39.– P.7445-7450.

7. *Yaragorla S.,Singh G., Dada R.* 'On water synthesis' of oxindoles bearing quaternary carbon center through C–H (sp^3) functionalization of methyl azaarenes// Tetrahedron Lett. – 2016.– Vol.57.– No. 5.– P.591-594.

8. *A catalyst-free*, one-pot, three-component approach for the synthesis of 2-[1-aryl-2-(azaaryl)ethyl]malononitriles via sp^3 C–H activation of 2-methyl azaarenes / Kumar N.S., Rao L.C., Babu N.J., Kumar V.D., Murthy U.S.N., Meshram H.M. // Synlett. – 2015.– Vol.26.– No. 13.– P.1808-1814.

9. *Functionalization* of tetra- and octahydroacridine derivatives through Michael addition / Zaliznaya E.V., Farat O.K., Varenichenko S.A., Mazepa A.V., Markov V.I. // Tetrahedron Letters. – 2016.– Vol.57.– No. 31.– P.3485-3487.

10. *Varenichenko S.A., Farat O.K., Markovm V.I.* Reactivity of substituted 2-spiropyrimidin-4-ones under Vilsmeier-Haack conditions // Chem.Heterocycl.Compd. – 2015. – Vol.50. – P.1602-1607.

11. *Синтез* похідних тетрагідроакридину в умовах реакції Вільсмайєра-Хаака / Фарат О.К., Залізна Е.В., Вареничeнко С.А., Марков В.І. // Питання хімії та хімічної технології. – 2020.– № 1. – С.92-96.

12. *SAR* of 9-amino-1,2,3,4-tetrahydroacridine-based acetylcholinesteraseinhibitors: synthesis, enzyme inhibitory activity, QSAR, and structure-based CoMFA of tacrineanalogues / Recanatini M., Cavalli A., Belluti F., Piazzi L., Rampa A., Bisi A., Gobbi S., Valenti P., Andrisano V., Bartolini M., Cavrini V. //

J. Med. Chem. − 2000. − Vol.43. − No. 10. − P.2007-2018.

13. *New* tacrine−huperzine a hybrids (huprines): highly potent tight-binding acetylcholinesterase inhibitors of interest for the treatment of Alzheimer's disease // Camps P., El Achab R., Morral J., Munoz-Torrero D., Badia A., Banos E.J., Vivas N.M., Barril X., Orozco M., Luque F.J. // J. Med. Chem. − 2000. Vol.43. − No. 24. − P.4657-4666.

14. *Hu M.-K., Lu C.-F.* A facile synthesis of bis-tacrine isosteres // Tetrahedron Lett. − 2000.− Vol.41.− P.1815-1818.

15. *The Vilsmeier-Haack*formylation of 2,3-dihydro-4H-1,3-benzoxazin-4-ones and isomeric 1,2-dihydro-4H-3,1-benzoxazin-4-ones: an effective approach to functionalized 2H-/4H-chromenes and tetrahydroacridines / Farat O.K., Markov V.I., Varenichenko S.A., Dotsenko V.V., Mazepa A.V. // Tetrahedron. − 2015.− Vol.71.− P.5554-5561.

Received 10.09.2020

ФУНКЦІОНАЛІЗАЦІЯ N-АРИЛМАЛЕЇМІДАМИ ЗА sp^3 С−Н ЗВ'ЯЗКУ ПОХІДНИХ ГІДРОАКРИДИНУ(ХІНОЛІНУ)

М.В. Сметанін, С.А. Вареничeнко, К.В. Залізна, О.В. Мазепа, О.К. Фарат, В.І. Марков

Було здійснено функціоналізацію N-арилмалеімідами за sp^3 С−Н зв'язком похідних тетрагідроакридину(хіноліну) в некаталітичних умовах за допомогою реакції Міхаеля. Цей метод забезпечує легкий синтез біологічно важливих N-арильних тетрагідроакридинових (хінолінових) фрагментів в одну стадію з високим виходом. Реакція протікає нагріванням гідроакридинів (хінолінів) у ДМСО в некаталітичних умовах протягом 4 год при 100−120^{0}С. В результаті взаємодії вихідних сполук було синтезовано (3S/4R)-3-[(3R/4S)-9-хлоракридин(хінолін)-4-іл]-1-(-N-арил)піролідин-2,5-діони з добрими виходами. Будову сполук було доведено спектральними методами аналізу. У спектрі ЯМР ^{1}Н характерними є сигнали протонів СН-груп акридинового(хінолінового) (3,4−3,5 м.ч.) та піролідинового (3,8−3,9 м.ч.) циклів. Цікаво відзначити, що основним напрямом фрагментації є ретрореакція Міхаеля, яка супроводжується елімінуванням 1-(2-нітрофеніл)-1Н-пірол-2,5-діону і приводить до утворення *m/z* іонів вихідних хлоракридинів(хінолінів).

Ключові слова: активація бензилового sp^3 С−Н зв'язку, некаталітичні умови, реакція Міхаеля, N-арилмалеіміди, похідні гідроакридину(хіноліну).

FUNCTIONALIZATION OF N-ARYLMALEIMIDES BY sp^3 C−H BONDS OF HYDROACRIDINES(QINOLINES)

N.V. Smetanin [a, *], S.A. Varenichenko [a], E.V. Zaliznaya [a], A.V. Mazepa [b], O.K. Farat [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: smetanin.nikolay13@gmail.com

The catalyst-free sp^3 C−H functionalization of tetrahydroacridine(quinolines) derivatives has been achieved using a Michael-type reaction with N-arylmaleimides. This method enables the facile synthesis of biologically important N-aryl bearing tetrahydroacridine(quinolines) moieties in a single step with high yields. The reaction occurs under non-catalytic conditions by heating of hydroacridines(quinolines) in DMSO within 4 h at 100−120^{0}C. The reaction between starting compounds allows synthesizing (3S/4R)-3-[(3R/4S)-9-chloroacridine(quinoline)-4-yl]-1(-N-aryl)pyrrolidine-2,5-diones with a good yield. The structure of compounds was proved by spectral methods of analysis. The ^{1}H NMR spectrum shows characteristic signals of protons of the CH-groups in acridine(quinoline) (3.4−3.5 ppm) and pyrrolidine (3.8−3.9 ppm) cycles. It is interesting to note that the main direction of the fragmentation is the Michael retro-reaction, which is accompanied by the elimination of 1-(2-nitrophenyl)-1H-pyrrole-2,5-dione and leads to the formation of *m/z* ions of starting chloroacridines(quinolines).

Keywords: benzylic sp^3 C−H activation; catalyst free; Michael reaction; N-arylmaleimides; hydroacridine(quinoline) derivatives.

REFERENCES

1. Komai H., Yoshino T., Matsunaga S., Kanai M. Lewis acid catalyzed benzylic C−H bond functionalization of azaarenes; addition to imines and enones.*Synthesis*, 2012, vol. 44, pp. 2185-2194.

2. Wang F.-F., Luo C.-P., Deng G., Yang L. C(sp^3)−C(sp^3) bond formation via copper/Bronsted acid co-catalyzed C(sp^3)−H bond oxidative cross-dehydrogenative-coupling (CDC) of azaarenes. *Green Chemistry*, 2014, vol. 16, pp. 2428-2431.

3. Liu J.-Y., Niu H.-Y., Wu S., Qu G.-R., Guo H.-M. Metal catalyzed C(sp^3)−H bond amination of 2-alkyl azaarenes with diethyl azodicarboxylate. *Chemical Communications*, 2012, vol. 48, pp. 9723-9725.

4. Li Y., Guo F., Zha Z., Wang Z. Iron-catalyzed synthesis of 2-vinylquinolines via sp^3 C−H functionalization and subsequent C−N cleavage. *Chemistry − An Asian Journal*, 2013, vol. 8, pp. 534-537.

5. Graves V.B., Shaikh A. Lewis acid-catalyzed Csp^3−H functionalization of methyl azaarenes with α-trifluoromethyl carbonyl compounds. *Tetrahedron Letters*, 2013, vol. 54, pp. 695-698.

6. Ershov O.V., Maksimova V.N., Lipin K.V., Belikov M.Yu., Ievlev M.Yu., Tafeenko V.A., Nasakin O.E. Regiospecific synthesis of gem-dinitro derivatives of 2-halogenocycloalka[b]pyridine-3,4-dicarbonitriles. *Tetrahedron*, 2015, vol. 71, pp. 7445-7450.

7. Yaragorla S., Singh G., Dada R. 'On water synthesis' of oxindoles bearing quaternary carbon center through C−H (sp^3) functionalization of methyl azaarenes. *Tetrahedron Letters*, 2016, vol. 57, pp. 591-594.

8. Kumar N.S., Rao L.C., Babu N.J., Kumar V.D., Murthy U.S.N., Meshram H.M. A catalyst-free, one-pot, three-component approach for the synthesis of 2-[1-aryl-2-(azaaryl)ethyl]malononitriles via sp^3 C−H activation of 2-methyl azaarenes. *Synlett*, 2015, vol. 26, pp. 1808-1814.

9. Zaliznaya E.V., Farat O.K., Varenichenko S.A., Mazepa A.V., Markov V.I. Functionalization of tetra- and octahydroacridine derivatives through Michael addition. *Tetrahedron Letters*, 2016, vol. 57, pp. 3485-3487.

10. Varenichenko S.A., Farat O.K., Markov V.I. Reactivity of substituted 2-spiropyrimidin-4-ones under Vilsmeier-Haack conditions. *Chemistry of Heterocyclic Compounds*, 2015, vol. 50, pp. 1602-1607.

11. Farat O.K., Zaliznaya E.V., Varenichenko S.A., Markov V.I. Synthesis of tetrahydroacridine derivatives through the Vilsmeier-Haack reaction. *Voprosy Khimii i Khimicheskoi Tekhnologii*, 2020, no. 1, pp. 92-96. (*in Ukrainian*).

12. Recanatini M., Cavalli A., Belluti F., Piazzi L., Rampa A., Bisi A., Gobbi S., Valenti P., Andrisano V., Bartolini M., Cavrini V. SAR of 9-amino-1,2,3,4-tetrahydroacridine-based acetylcholinesterase inhibitors: synthesis, enzyme inhibitory activity, QSAR, and structure-based CoMFA of tacrine analogues. *Journal of Medicinal Chemistry*, 2000, vol. 43, pp. 2007-2018.

13. Camps P., El Achab R., Morral J., Munoz-Torrero D., Badia A., Banos E.J., Vivas N.M., Barril X., Orozco M., LuqueF.J. New tacrine−huperzine a hybrids (huprines): highly potent tight-binding acetylcholinesterase inhibitors of interest for the treatment of Alzheimer's disease. *Journal of Medicinal Chemistry*, 2000, vol. 43, pp. 4657-4666.

14. Hu M.-K., Lu C.-F. A facile synthesis of bis-tacrineisosteres. *Tetrahedron Letters*, 2000, vol. 41, pp. 1815-1818.

15. Farat O.K., Markov V.I., Varenichenko S.A., Dotsenko V.V., Mazepa A.V. The Vilsmeier−Haack formylation of 2,3-dihydro-4H-1,3-benzoxazin-4-ones and isomeric 1,2-dihydro-4H-3,1-benzoxazin-4-ones: an effective approach to functionalized 2H-/4H-chromenes and tetrahydroacridines. *Tetrahedron*, 2015, vol. 71, pp. 5554-5561.