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SYNTHESIS OF NEW DERIVATIVES OF FUNCTIONALLY SUBSTITUTED CYCLOBUTANECARBOXYLIC ACIDS AS POTENTIAL NEUROMODULATORS

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Based on functionally substituted cyclobutanecarboxylic acid constructed by the method of Atom Transfer Radical Cyclization (ATRC) of polyhalogenhexenoic acid in the presence of the copper(I) amine complexes, two new derivatives were synthesized. Their structural features - gem-dimethyl, trichloromethyl and carboxyl groups attached directly to small strained carbocycles make them potentially active as agonists for neural sodium channels, as well as GABA and NMDA receptors.

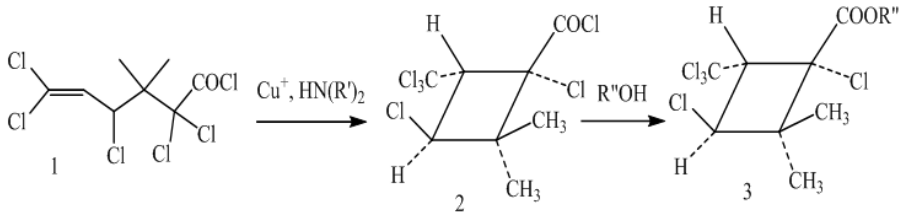
Ref. 5., schem. 2.

Keywords: cyclobutane derivatives, building blocks, ATRA, α-halogen alkenoic acids, piperidine

Cyclobutanecarboxylic acids and their derivatives are present as structural units in various biologically active molecules [1, 2]. The derivatives of these molecules themselves are potential candidates for binding to specific receptors in the brain, as well as for modulating the activity of the GABA or NMDA receptors, which is extremely important for the search for new drugs for the treatment of specific neurological diseases [3]. The response activated by NMDA agonists is unique in that it exhibits a voltage-dependent ion-channels block and, as is well known, this response exhibits another remarkable property - it is dramatically potentiated by glycine. So, the cyclic homologue of glycine,

l-aminocyclobutane-1-carboxylate (ACBC), has been reported to exhibit activity at this glycine site. It was shown to act concurrently as a glycine site partial agonist and as a glutamate site antagonist, thus protecting against neural cell death and exhibiting antipsychotic-like effects in animal models.

The development of new catalytic enantio- and diastereoselective methods for the synthesis of cyclobutane would be a valuable tool for the synthetic chemists and drug designers for elaboration of novel routes for constructing cyclobutane-based physiologically active structures. From this point of view, elaboration of new technologies for the synthesis of cyclobutanecarboxylic acids with different structure modifications is a very important task. In our laboratory the generic method for construction of substituted cyclobutane-carboxylic acids was developed based on transition metal-catalyzed intramolecular cyclization reaction of α-halogen-containing alkenoic acids via Atom Transfer Radical Cyclization (ATRC) [4] (Scheme 1).

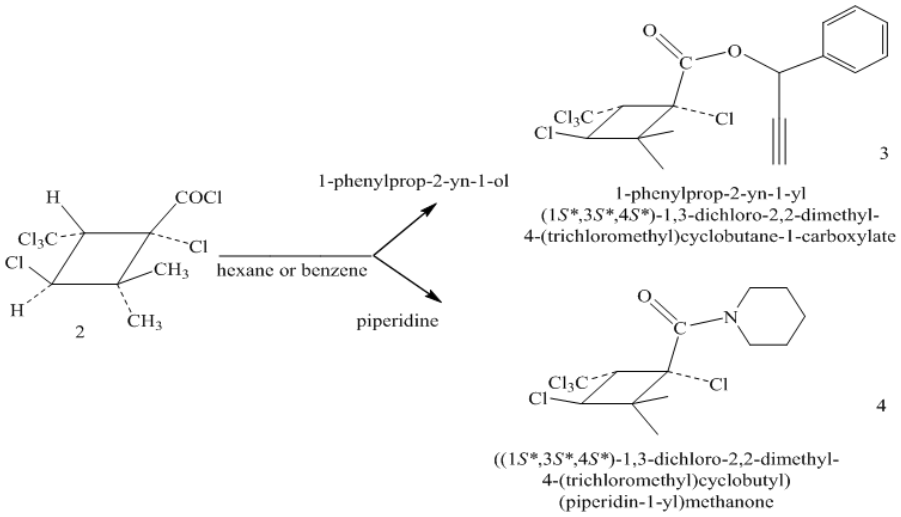


Scheme 1. Stereo controlled pathway for cyclobutane construction

It was determined that the stereoisomeric composition of the cyclobutane derivatives depended on the nature of the functional groups in the initial α-dichloroalkenoic acids and was featured to involve in the coordination sphere of transition metals ion [4].

Thus, elaboration of future synthetic technique on the basis of the synthesized cyclobutanecarboxylic acids (2 or 3) with skeletal feature can lead to a number of cyclic compounds with potentially high biological activity. In this paper, synthetic procedure and physicochemical, spectral characteristics of two new derivatives (with relative configuration corresponding to 3 and 4) are presented (Scheme 2).

The presence of a weak base (pyridine or piperidine) in the reaction system, even in excess amount, is not enough for parallel or consequent dehydrochlorination of substrate, conditioned by high acidity of of the neighboring H- atom at CCl_3 group [5].



Scheme 2. Derivatization of cyclobutanecarboxylic acid chloride

The structure of synthesized new derivatives of cyclobutane series **3** and **4** was established from the data of NMR spectra and via comparison of appropriate spectral characteristic of analogue cyclobutane scaffoldings [4]. These data obviously showed that the derivitization of cyclobutane carboxylic acid chloride **3** proceeded without any epimerization of 3 chiral centers in the cyclobutane ring. This is also evidenced by the vicinal coupling constants value: J (H, H) ~10 Hz of hydrogen atoms bonded at cyclobutane ring in the trans-location of two new derivatives. This was also confirmed by NOEDIF experiments: in ^{1}H NMR spectra low field signal corresponded to methyl group located in the *trans*-position with respect to the trichloromethyl substituent. The relative configuration of trichloromethyl and carboxy group was determined by the absolute value of the vicinal $^{3}J_{trans}$(^{13}C, ^{1}H) coupling constant.

It should be noted that as opposed to the earlier obtained analogue of cyclobutane structures [4], in mass-spectrum of **3** ester (1-Phenylprop-2-yn-1-yl) we can observe molecular-ion picks of minor intensity (2%). We thought that with the increase of molecular mass of investigated carbocycles, the relative stability of the observed substances to ionizing impact will increase too.

Experimental

Reaction monitoring, chromatographic analysis of the starting and synthesized compounds were carried out on a gas chromatograph - Agilent Technologies GC-7809B, capillary column - DB-WAX-30 *m*-320 μm x 0.25 μm, FID detector, detector temperature 300°*C*, injector temperature 250 °*C*, flow rate gas (N_2) 6 *ml/min*, column temperature 40 °*C* hold for 2 *min*, 7 °*C/min*

235 °*C* hold for 5 *min*. The mixture of reactants was separated by column and preparative chromatographic methods. Column chromatography was performed in a glass column, 200-700 *mm* high, 25 *mm* in diameter, filled with silica gel L40/100, eluent was diethyl ether/hexane in a ratio of 1:20. The components of the mixture were separated by a selective method of light absorption of ultraviolet rays (UV-254) TLC analyses were carried out using Silufol UV-254 plates. Visualization was carried out in the presence of iodine vapor and a solution of potassium permanganate. Melting points were measured on a Fisher-Johns device.

The NMR spectra were registered on a spectrometer Varian Mercury-300 at operating frequencies 300.077 MHz (^{1}H), 75.46 MHz (^{13}C), chemical shifts were reported with respect to TMS. The signal assignment in the ^{1}H and ^{13}C NMR spectra was performed with the use of methods NOEDIF, HMQC, and by registering ^{13}C NMR spectra without decoupling from protons. Mass spectra were obtained on an instrument MKh-1320, energy of ionizing electrons 70 *eV*.

1-Phenylprop-2-yn-1-yl(1S*,3S*,4S*)-1,3-dichloro-2,2-dimethyl-4(trichloro-methyl)cyclobutane-1-carboxylate (3). To the solution of cyclobutane-1-carboxylic acid chloride **2** (3.33 *g*, 10 *mmol*) in anhydrous benzene (10 *ml*), the mixture of 1-phenyl-propargyl-alcohol (1.32 g, 10 *mmol*) and pyridine (0.79 *g*, 10 *mmol*) dissolved in anhydrous benzene (10 *ml*), was added dropwise at room temperature with vigorous stirring.

The mixture was stirred for 5h at 25 °*C*. The reaction was monitored by GC and TLC. The mixture was filtered; the filtrate was diluted with diethyl ether (10 *ml*), washed with water (2-5 *ml*) and dried over $MgSO_4$. The solvents were removed and 3.82 *g* of raw product was obtained. After purification on a column (1.8 x 50 *cm*, silica gel 40 *g*, eluent-hexane: ether =10:1), 2.95 *g* (69 %) of **3** ester was isolated in the form of colorless crystals, mp=115-117 °*C*. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.00 (3H, s, *cis*-H_3CC–CCOO-); 1.30 (3H, s, *trans*-H_3CC–CCOO-); 2,74 (1H, d, *J*=2.40, ≡CH); 4.39 (1H, d, *J*=9.86, CHCl); 4.52 (1H, d, *J*=9.86, $CHCCl_3$); 6.53 (1H, d, *J*=2.40, OCH); 7.38-7.61 (5H, m, C_6H_5).^{13}C (75.5 MHz, $CDCl_3$) δ, ppm: 166.0; 135.5; 129.7; 128.9; 128.2; 95.3; 78.9; 76.8; 70.4; 68.1; 62.4; 59.7; 47.4; 23.0; 20.7. Mass-spectra, m/z (I_{rel},%): 430 $[M]^+$ (1), 430 $[M]^+$ (2), 428 $[M]^+$ (2), 426 $[M]^+$ (2), 395 $[M\text{-}Cl]^+$ (2), 393 $[M\text{-}Cl]^+$ (2), 391 $[M\text{-}Cl]^+$ (1), 131 (3), 116 (8), 115 (100), 114 (25), 90 (4).

((1S*,3S*,4S*)-1,3-dichloro-2,2-dimethyl-4-(trichloromethyl)cyclobutyl)(pipe-ridin–1-yl)methanone (4). To the solution of cyclobutane-1-carboxylic acid chloride **2** (3.33 *g*, 10 *mmol*) in absolute hexane, 1.68 *g* (20 *mmol*) of pyridine was added dropwise over 10 minutes. The temperature rose to approximately 35 °*C*. Then the mixture was stirred for 3 *h* at 35-40 °*C*. The progress of the reaction was monitored by GC and TLC methods, then 5ml of water was poured to the mixture. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3-10 *ml*). The ether extract was washed with

water, added to the organic layer and dried over anhydrous $MgSO_4$. Solvents were removed, colorless crystals were obtained, which were recrystallized (hexane/ether=10:1). Piperidylcarboxamide **4** was obtained 2.78 *g* (73%), mp.=154-156 °*C*. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, s, *cis*-$H_3CC–CCN_{piperidyl}$); 1.42 (3H, s, *trans*-$H_3CC–CCN_{piperidyl}$);1.5-1.8 (6H, m, -CH_2-CH_2-CH_2-); 3.15-3.84 (4H, m, -CH_2-N-CH_2-); 4.54 (1H, d, *J*=11, -CHCl,); 4.82 (1H, d, *J*=11, $CHCCl_3$). ^{13}C NMR spectrum, δ, ppm: ($CDCl_3$): 165.0, 77.6, 77.2, 76.7, 72.6, 62.4, 62.4, 59.9, 47.3, 46.9, 44.9, 25.9, 25.7, 24.4, 23.2, 21.1; 28.2; 95.3; 78.9;76.8; 70.5; 68.1;62.4; 59.7; 47.4; 23.0; 20.7.

ՈՐՊԵՍ ՊՈՏԵՆՑԻԱԼ ՆԵՅՐՈՄՈԴՈՒԼՅԱՏՈՐՆԵՐ ՖՈՒՆԿՑԻՈՆԱԼ ՏԵՂԱԿԱԼՎԱԾ ՑԻԿԼՈԲՈՒԹԱՆԿԱՐԲՈՆԱԹԹՈՒՆԵՐԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶԸ

Ա. Բ. ԲԱՂԴԱՍԱՐՅԱՆ, Ա. Մ. ԳՐԻԳՈՐՅԱՆ, Ա. Ռ.ՄԻՔԱԵԼՅԱՆ

Պղնձի(Ι) ամինային կոմպլեքսների ներկայությամբ պոլիհալոգենհեքսենաթթվից ATRC *(Ատոմի Փոխանցմամբ Ռադիկալային Ցիկլացում) մեթոդով ստացված ֆունկցիոնալ տեղակալված ցիկլոբութանկարբոնաթթուների կառուցվածքային հենքի վրա սինթեզվել են երկու նոր ածանցյալներ: Փոքր լարված կարբոցիկլում հեմ-դիմեթիլ, տրիքլորմեթիլ և կարբոնիլ տեղակալիչների առկայությունը դարձնում են դրանց պոտենցիալ ակտիվ նատրիումի իոնների նյարդային անցուղիների,* GABA *և* NMDA *ընկալիչների նկատմամբ:*

СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ ФУНКЦИОНАЛЬНО ЗАМЕЩЕННЫХ ЦИКЛОБУТАНКАРБОНОВЫХ КИСЛОТ КАК ПОТЕНЦИАЛЬНЫХ НЕЙРОМОДУЛЯТОРОВ

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На основе функционально замещенной циклобутанкарбоновой кислоты, сконструированной методом ATRC (Радикальная Циклизация с Переносом Атома) полигалогенгексеновой кислоты в присутствии аминных комплексов меди(I) синтезированы две новые производные. Структурные особенности: гем-диметильные, трихлорметильные и карбонильные группы, присоединенные непосредственно к малым напряженным карбоциклам, делают их потенциально активными в качестве агонистов нервных натриевых каналов и рецепторов GABA, NMDA.

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