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Synthesis, spectroscopic characterization and DFT calculations of monohydroxyalkylated derivatives of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione

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ABSTRACT

Synthesis of new derivatives with an imidazo[1,5-*c*]quinazoline-3,5-dione ring has been presented. Two new alcohols with the imidazo[1,5-*c*]quinazoline-3,5-dione ring were obtained and characterized by spectral (^{1}H, ^{13}C NMR, IR and UV) and crystallography methods. A reaction chemoselectivity has been observed with a formation of monohydroxyalkyl derivatives of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione substituted at the 2. nitrogen atom. The absence of derivatives substituted at the 6. nitrogen atom was proven experimentally. The synthesis with chemoselectivity over 99% without control of the substituent effect happens very rarely. The HOMO–LUMO mappings are reported which reveals the different charge transfer possibilities within the molecule of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione in the region of the 2. and the 6. nitrogen atoms. Quantum-mechanical DFT calculations proved to be very useful to explain the reason of selectivity reaction of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione with oxiranes.

1. Introduction

Compounds containing imidazoquinoline and imidazoquinazoline moieties have been reported to possess interesting properties [1–3]. Until now, more than one hundred of imidazo[4,5-*c*]quinolin-2-one derivatives have been described in scientific literature and, at least, half of them exhibit various aspects of biological activity [3]. Recently, due to their biological importance, there has also been a great interest in 3,3-disubstituted quinoline-2,4-diones, such as, for example 3-azidoquinoline-2,4-dione and 3-hydroxy-3-alkylquinoline-2,4-dione. The first compound behaves as platelet aggregation inhibitor, whereas the second one was found in bacteria with antibiotic properties [4].

Combining the imidazole and quinazoline moieties leads to the formation of imidazoquinazolines – a group of compounds widely applied in pharmacy and medicine due to their versatile biological properties. This includes an antitumor, antiviral, antibacterial and anticonvulsant action (there are drugs containing imidazoquinazoline ring currently available on the market) [5]. Furthermore, some other derivatives belonging to this group of compounds can also be used to neutralize free radicals, and as a consequence, to prevent lipid peroxidation and cell damage [6].

In addition to the above-mentioned properties and applications, some of the imidazoquinazolines [7] also exhibit a high thermal stability, e.g. 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione, which makes them potential substrates for synthesis of thermally stable polymers. The decomposition temperature of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione (Fig. 1) exceeds 400 °C (see Results and discussion).

Polymers of a high thermal stability do not degrade during a long term use (up to 25,000 h) at a temperature lower than 300 °C. They also stay stable during a short-time heating (up to 300 h) at a temperature of 500 °C keeping the shape of the polymer unchanged and staying solid [8,9]. It should be noted that the most of

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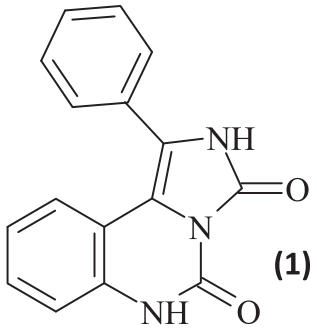

Fig. 1. The structure of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione.

polymers with improved thermal stability consist of aromatic or heterocyclic rings [10].

Taking into account the fact that there is a high demand for thermally stable polymers, more and more research is conducted involving the synthesis and study of the properties of materials of enhanced thermostability [11–15].

In the present work, the synthesis of two monohydroxyalkylated derivatives of compound (1) will be described. These compounds can be the precursors in the production of thermally stable polymers, e.g. polyurethanes. The synthesis reactions of new alcohols with imidazoquinazoline ring have proven to be highly chemoselective. To rationalise this phenomenon, the quantum chemical calculations have been performed using the density functional theory (DFT).

2. Results and discussion

2.1. Thermal stability of 1-phenyl-2H,6H-imidazo[1,5-c] quinazoline-3,5-dione

The performed analysis confirmed the high thermal stability of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione (Fig. 2). 1% and 5% weight loss occurred at temperature of 390 and 420 °C, respectively (Fig. 2).

The DTG (*Derivative Thermogravimetric Analysis*) curve exhibits one peak only at a temperature of 460 °C. At the same temperature, the DTA (*Differential Thermal Analysis*) curve shows an endothermic peak derived from the complete decomposition of the compound.

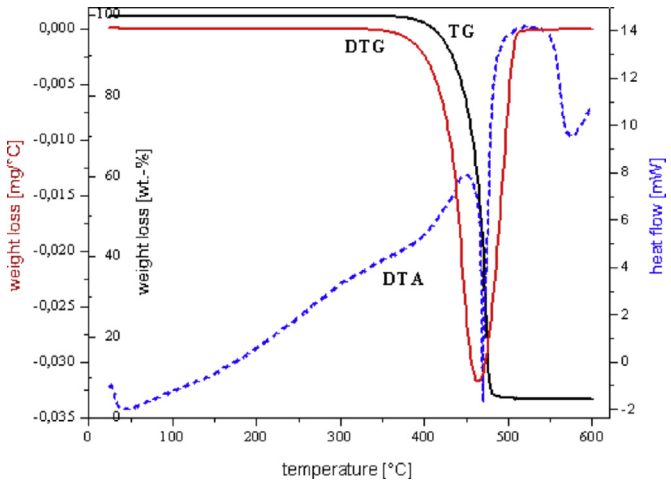

Fig. 2. Thermal analysis of 1-phenyl-2*H*,6*H*-imidazo[1,5-*c*]quinazoline-3,5-dione.

2.2. Synthesis of new alcohols with imidazoquinazoline ring

Compound (1) is almost insoluble in water and organic solvents. It is poorly soluble in hot *N*,*N*-dimethylformamide (0.3 g/100 g) and DMSO (1.5 g/100 g). Therefore, it is important to obtain its derivatives showing much better solubility. This would allow the incorporation of the imidazoquinazoline ring in the polymer chains.

In order to obtain such derivatives, compound (1) underwent hydroxyalkylation reaction with oxiranes. The compound (1) was reacted with ethylene oxide (EO) or propylene oxide (PO) in the presence of triethylamine (TEA) as a catalyst at a temperature of 60–90 °C (Table 1).

These both reactions are thermodynamically controlled as typical reaction with oxiranes [16,17]. In the reaction of an equimolar amount of compound (1) and EO a novel monohydroxyethyl derivative substituted at the 2. nitrogen atom was obtained (Fig. 3).

Compound (2) is a white crystalline solid with a melting point of 320–321 °C. The compound (2) was characterized by different instrumental methods (see Experimental Part).

Similarly, the reaction of compound (1) with PO was performed (Fig. 4).

The use of equimolar amounts of these reagents gave the N(2)-substituted derivative, i.e. compound (3) with a melting point of 283–284 °C. The structure of this product (3) was confirmed by instrumental techniques (see Experimental Part).

2.3. Spectral characteristic of new alcohols with imidazoquinazoline ring

In the ^{1}H NMR spectrum of (1), in addition to the proton signals of the phenyl ring and quinazoline, two signals of amide protons are observed at 10.6 ppm and 11.15 at the 6. nitrogen atom and the 2. nitrogen atom, respectively. In the ^{1}H NMR spectrum of the compound (2) (Fig. 2S), only one signals is observed in this region, at 10.65 ppm from the proton of the 6. nitrogen atom. It indicates the substitution the proton at the 2. nitrogen atom upon equimolar reaction of (1) and ethylene oxide. Similar changes are observed in the spectrum (Fig. 6S) of the equimolar reaction product of compound (1) with propylene oxide.

Substitution at the 2. nitrogen atom results in a change of the position of imidazoquinazoline ring protons in the ^{1}H NMR spectra (compare Experimental Part, Figs. 2S and 6S and the paper [7]). Furthermore, there are two triplets of the chemical shift of 3.40 and 3.47 ppm due to protons of methylene groups, respectively at the nitrogen atom and the oxygen atom of 2-hydroxyethyl group, in the ^{1}H NMR spectrum of the product (2). Proton signal of the hydroxyl groups is observed at 4.81 ppm.

In the ^{1}H NMR spectrum of the product (3), the proton signals of the methyl group, the methine group and signals of diastereotopic protons of the methylene are observed. The latter signals overlaps to the signal derived from the water present in the solvent, similar situation was described in paper [18].

NMR spectra allow to measure the interproton coupling constants of compounds (2) and (3). The coupling constants show the typical values. In turn, the values of coupling constants of (3) calculated by DFT method using two different bases are completely different from the values measured by NMR (Table 5S). The exception is only one value of the coupling constant - $J_{8,9}$. In this case, both values are almost identical.

^{13}C NMR spectra of compounds (2) and (3) also confirm their structure. Besides signals derived from carbon atoms of phenyl and imidazoquinazoline rings, also signals of carbon atoms of methylene groups of (2) and carbon atoms of the methyl, methylene and methine groups of (3) are observed (Figs. 3S and 7S).