Nuclear-Chemical Synthesis of 1,4-Diazine Quaternary Salts

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Received December 3, 2012; revised February 2, 2013; accepted February 21, 2013

ABSTRACT

Ion-molecular reactions of nucleogenic phenyl cations with the nucleophilic centers of 1,4-diazines have been investigated for the first time. Previously unknown tritium labeled N-phenyl quaternary derivatives of pyrazine and quinoxaline, which are potential radioactive biomarkers, have been obtained by nuclear-chemical method.

Keywords: Nucleogenic Phenyl Cations; 1,4-Diazines; Quaternization; Tritium Labeling

1. Introduction

Diazines attribute to the six-ring heterocycles with two heteroatoms both of which are nitrogen atoms. Cyclic pyrazine system forms common structural fragment of 1,4-diazines. Benzopyrazine or quinoxaline has pyrazine cycle annulated with the benzene ring. 1,4-Diazines and condensed systems with pyrazine ring are known as an important type of heterocyclic derivatives with high biologic activity [1-4]. Synthetic pyrazines exhibit a wide range of physiological activities including antibacterial, antitubercular, antiprotozoal and antitumor [5-9]. These promising results stimulate chemists and biologists for further research in the field of pyrazine derivatives over the last few years [10-22].

Modern progress in biology, biochemistry and molecular genetics along with the experimental medicine is largely determined by the wide application of labeled, especially tritium labeled compounds, for the sensitive direct studies of the biochemical reaction mechanisms and metabolic pathways of the essential pharmaceuticals [23-36].

Owing to this the development of easy and unusual methods for synthesis of new 1,4-diazine derivatives along with tritium labeling becomes an urgent task. Previously we have applied the elaborated nuclear-chemical method based on the consequences of tritium β-decay for the one-step preparation of unknown and hardly available derivatives of monoazines, effective tritium labeled biological markers [37-41].

2. Experimental

2.1. Tritium Double Labeled Benzene

Benzene double labeled with tritium was obtained from 1,4-dibromobenzene (3.4 mg, 0.014 mmol), and n-Bu3N (5.0 µl, 0.020 mmol) in hexane, tritium gas (3.3 Ci, 0.054 mmol) by dehalogenation on a 5% Pd/BaSO4 catalyst for 1 h at room temperature [39]. The chemical purity of the synthesized doubly labeled benzene was not less than 99%. Analysis of tritium-labeled benzene was carried out by gas chromatography. The volume specific activity of the obtained solution in hexane was 1 Ci/ml.

2.2. Nuclear-Chemical Synthesis

Crystals of the stabilizing salt KBF4 (~200 mg) were placed in 0.5 ml glass ampoules, then 0.055 mmol of substrates: pyrazine (4.4 mg,) or quinoxaline (7.2 mg) dissolved in ether were placed on the salt crystals. The ether was distilled off in vacuum, and after cooling the ampoules with liquid nitrogen, a C6H4T2 hexane solution (1 µl) was added. The C6H4T2 concentration was selected so that the ratio of labeled benzene to substrate was not less than 1:1000. The ampoules were sealed, and stored for 1 - 2 months at ~15°C for accumulation of the nuclear-chemical synthesis products. The ampoules were opened, the contents were transferred to special vials,
and benzene (0.5 ml) was added, followed by the carrier acetone solution (0.5 ml), (1 mg/ml). Due to the absence of isotopic carriers the unlabeled N-phenylpyridinium and quinolinium salts [37,42] were used. Unreacted C₆H₄T₂ was removed by distillation in vacuum. Acetone (0.5 ml) was added to the dry residue and samples (about 5 µl) were taken for isolation of labeled compounds by TLC.

2.3. TLC Radiochromatography

Radiochromatography of the obtained tritiated compounds was carried out on glass plates with Analtech TLC Uniplates C18 Reverse Phase silica gel (Fluorescent Indicator) in MeCN. Bands of the chromatographic adsorption layer measuring 0.5 cm in length were removed into dioxane scintillator and their β-radioactivity measured with the aid of a Rack Beta (Finland) liquid scintillation counter. Typical radiochromatograms are shown on Figures 1 and 2.

First peaks on the radiochromatograms correspond to the quaternary salts. Relative yields of ion-molecular reactions products were determined as a ratio of the radioactivity of an individual compound towards the sum of all tritium labeled products.

3. Results and Discussion

Generation of nucleogenic phenyl cations (cations formed by radioactive decay) occurs by spontaneous β-decay of tritium in the labeled benzene. Nuclear-chemical method provides unique opportunity for unusual formation of carbocations along with the several essential advantages: 1) obtained phenyl cations are free, that means without counterion; 2) investigated ion-molecular reactions take place on the surface of stabilizing salt without a solvent; 3) all reactions are carried out in the very mild conditions since decay processes are independent from temperature, pressure and so on.

The presence of at least two atoms of tritium in the benzene molecule leads to the preparation of cations labeled with tritium (Scheme 1).

The proposed scheme (Scheme 2) for the ion-molecular interactions of nucleogenic phenyl cations with quinoxaline (for example) may be represented in the following manner.

Upon the interactions of free phenyl cations with the investigated diazines, quaternary salts are formed by AdE (electrophilic addition) as well as substitution products formed by Se (electrophilic substitution) are produced.

The radiochemical yields of the quaternary salts for the investigated 1,4-diazines are shown in Table 1. Pyrazines have considerable aromatic character; therefore their main reactivity pathways can be predicted by regarding them as pyridines which have a nitrogen atom in the para-position.

Nitrogen atom in azines possesses a pair of electrons, which is not involved in the formation of σ or π bonding orbitals. Those electrons may form a bond between the

\[
\text{C}_6\text{H}_4\text{T}_2 \xrightarrow{\beta-\text{decay}} \text{C}_6\text{H}_4\text{T}^+ + ^3\text{He}
\]

Scheme 1. Generation of nucleogenic phenyl cations.

\[
\text{C}_6\text{H}_4\text{T}^- + \text{C}_6\text{H}_4\text{T}^+ \xrightarrow{\text{AdE}} \text{C}_6\text{H}_6\text{T}_2^+
\]

\[
\text{C}_6\text{H}_4\text{T}^- + \text{X}^- \xrightarrow{\text{Se}} \text{C}_6\text{H}_5\text{X}^+
\]

Scheme 2. Pathways of ion-molecular interactions of nucleogenic phenyl cations with quinoxaline.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield of quaternary salt (AdE), %</th>
</tr>
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<tbody>
<tr>
<td>Pyrazine</td>
<td>4.0% ± 0.5%</td>
</tr>
<tr>
<td>Quinoxaline</td>
<td>6.0% ± 0.5%</td>
</tr>
</tbody>
</table>

Table 1. Radiochemical yields of the quaternary salts.
The authors gratefully acknowledge the financial support previously unknown nucleogenic phenyl cations in 1,4-diazines, furnishing a new way of the direct nitrogen atom phenylation by the elaborated nuclear-chemical method of synthesis enables ring closure. We have extended our elaborated nuclear-chemical method for the direct phenylation of nitrogen atom in 1,4-diazines. In spite of relatively small radiochemical yields of \(N\)-phenyl quaternary derivatives of pyrazine and quinoxaline (Table 1) it may be considered as a first step in the new field of previously unknown \(N\)-aryl quaternary diazine compounds. Use of free nucleogenic phenyl cations may also lead to the formation of diquaternary derivatives (the second peaks on the radiochromatograms). In the case of quinoxaline (Figure 2), several peaks can be attributed to the products of electrophilic substitution into the benzene ring. This theory is further collaborated by the comparison between quinoxaline and pyrazine diagrams (Figures 1 and 2 correspondently).

Further research will be undertaken for the detail investigations of ion-molecular interactions of nucleogenic phenyl cations with the nucleophilic centers of 1,4-diazines.

4. Conclusion

Elaborated nuclear-chemical method of synthesis enables a new way of the direct nitrogen atom phenylation by the nucleogenic phenyl cations in 1,4-diazines, furnishing previously unknown \(N\)-phenyl quaternary derivatives.

5. Acknowledgements

The authors gratefully acknowledge the financial support of the Russian Foundation for Basic Research (Project No. 10-03-00685a).

REFERENCES


