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Synthesis of Difluorobenzene Double-Labeled with Tritium

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Abstract—A procedure based on nuclear-chemical generation of free nucleogenic reactive species was developed for the synthesis of difluorobenzene double-labeled with tritium as a precursor for the generation of previously unknown difluorophenyl cations.

Keywords: difluorobenzene, tritium-labeled compounds, nuclear-chemical generation of carbenium ions

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The nuclear-chemical method, discovered in the middle of the XX century, offers a unique opportunity to generate free carbenium ions by β-decay of tritium in hydrocarbons [1–3]. Previously we performed a series of studies on generation of nucleogenic phenyl cations by β-decay of tritium both in fully tritiated benzene,

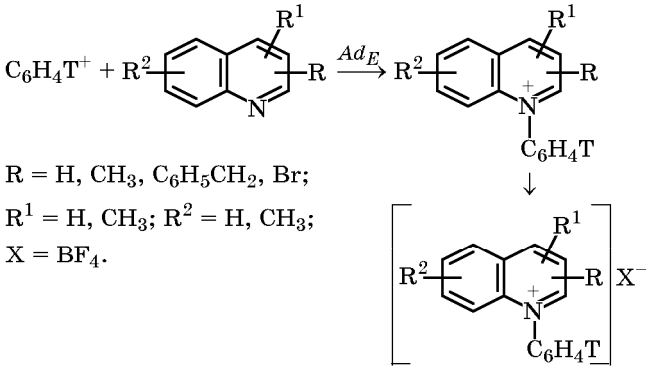
$$C_6T_6 \xrightarrow{\beta^-} [C_6T_5{}^3He]^+ \rightarrow C_6T_5^+ + {}^3He,$$

and in ditritiobenzene,

$$C_6H_4T_2 \xrightarrow{\beta^-} C_6H_4T^+ + {}^3He.$$

We also studied ion–molecule reactions of the generated free nucleogenic phenyl cations with various classes of polycentered nucleophiles: organic, organometallic, and heterocyclic compounds [4–6].

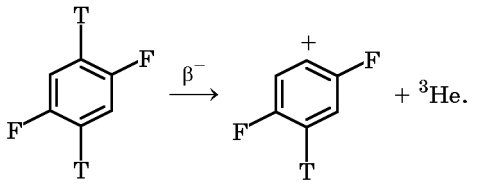
A significant achievement of the nuclear-chemical method was the discovery of the previously unknown reaction of direct phenylation of the nitrogen atom in six-membered heterocyclic derivatives (this particularly concerns quinolinium derivatives)



and the development of a one-step route to unknown and difficultly accessible tritium-labeled *N*-phenyl heterocyclic onium compounds, many of which are important biologically active substances [7, 8].

Six-membered nitrogen-containing heterocyclic compounds are extremely important objects of biological studies. Among these compounds are natural nicotinic acid derivatives (coenzymes, vitamins B_2 and B_6). Enormous number of drugs contain a heterocyclic pyridine ring (Piroxicam exhibiting anti-inflammatory activity, Nifedipine and Amlodipine used for the treatment of stenocardia, and Pinacidil used for treatment of hypertonic disease) [9–11]. Introduction of fluorine into the quinoline ring led to the discovery of a new class of strong antibacterial drugs, those of the fluoroquinolone series, occupying a prominent place among modern antibacterial chemotherapeutic agents [12–19].

In this connection, it was of particular interest to perform nuclear-chemical syntheses of fluorinated heterocyclic derivatives. To introduce fluorine into the benzene ring, we chose a new reactive species, fluorinated phenyl cation, which will be generated by the β-decay of tritium in difluoroditritiobenzene:



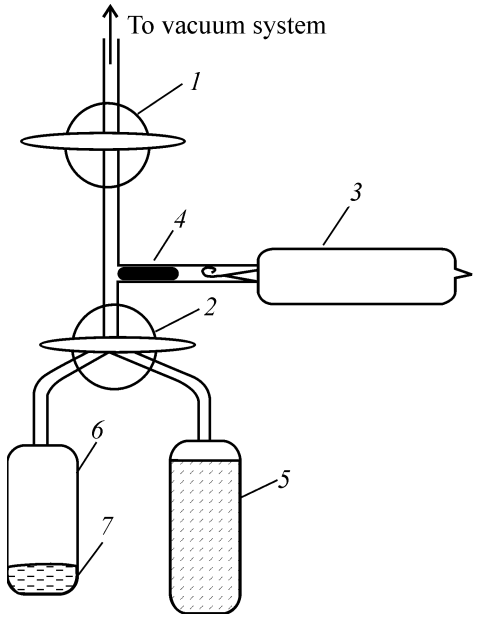
In so doing, to generate a single kind of cations, it is necessary to choose a difluoroditritiobenzene with equivalent tritium atoms. This requirement is met in

two difluoroditritiobenzene isomers: 1,4-difluoro-2,5-ditritiobenzene and 1,2-difluoro-4,5-ditritiobenzene.

Difluoroditritiobenzene can be prepared via two alternative pathways: hydrolysis of difluorophenylenedilithium [20] with tritium-containing water and catalytic replacement of halogen by tritium [21] in difluorodibromobenzene. The disadvantages of the first pathways are the need for using large excess of tritium-containing water in hydrolysis and for performing the reaction in diethyl ether, which is a strong nucleophile and hence will compete with quinoline compounds in reactions with difluorophenyl cation. Removal of excess tritium-containing water and replacement of the ether by a weak nucleophile, hexane, are undesirable in operation with ultrasmall amounts of labeled compounds. The second pathway is free of these drawbacks, and specifically this pathway was chosen for the synthesis of difluoroditritiobenzene. Difluoroditritiobenzene was synthesized by the modified procedure involving halogen replacement by tritium, catalyzed by $Pd/BaSO_4$, in the presence of an amine for binding the released hydrogen halide:

$$C_6H_2F_2Br_2 + 2^3H_2 + (C_4H_9)_3N \rightarrow C_6H_4F_2{}^3H_2 + (C_4H_9)_3N^3H^+Br^-.$$

The synthesis was performed on an installation schematically shown in the figure. As starting compound we used 1,4-dibromo-2,5-difluorobenzene, and as a base for binding HBr, high-boiling tributylamine, which allowed easy separation of difluorobenzene and amine by simple vacuum distillation. The reaction ampule was charged with 5–10 mg of the catalyst (5% $Pd/BaSO_4$), a second ampule was charged with CaX molecular sieves, and both ampules were connected to a synthesis installation. Ampules with molecular sieves and with the catalyst were evacuated with heating to ~400 and ~160°C, respectively. The evacuation was continued until the maximal rarefaction (~10^{-3} mm Hg) was attained. After that, hydrogen was admitted into the ampule with the catalyst to a pressure of ~0.5 atm. The ampule was kept for 10–15 min at ~160°C and cooled to room temperature, after which the residual hydrogen and volatile hydrogenation products were removed in a vacuum. Then the reaction ampule was detached, and 50 μl of a hexane solution containing 20 μmol of 1,4-dibromo-2,5-difluorobenzene and 30 μmol of tributylamine was introduced. The ampule was cooled with liquid nitrogen and evacuated. Into the ampule with molecular sieves, cooled with liquid nitrogen, 2.5 Ci of tritium was condensed. The three-way stopcock was arranged in the position in which the reaction ampule was connected with the ampule containing molecular sieves. The reaction ampule was cooled with liquid nitrogen, and the ampule with molecular sieves was allowed to warm up to room temperature. After that, the three-way stopcock was turned to seal the ampule with the molecular sieves, and its contents were agitated by shaking for 1 h. The ampule with the molecular sieves was replaced by a clean empty ~0.5 cm^3 ampule. The reaction ampule was evacuated with cooling with liquid nitrogen, and volatile hydrogenation products together with hexane were distilled in a static vacuum into the newly attached ampule cooled with liquid nitrogen.



Scheme of the installation for the synthesis of difluoroditritiobenzene: (*1*) vacuum stopcock, (*2*) three-way stopcock, (*3*) ampule with tritium, (*4*) magnetic striker, (*5*) ampule with molecular sieves, (*6*) reaction ampule, and (*7*) reaction mixture and catalyst.

The reaction products were analyzed by gas chromatography. In the chromatogram, there were only two peaks belonging to hexane and difluorobenzene, suggesting high chemical purity of the product obtained. Its amount was determined by external normalization to be 14.6 μmol, which corresponds to 73% yield based on 1,4-dibromo-2,5-difluorobenzene. The activity of the product was measured by liquid β-ray radiometry with a Beta-2 installation. The synthesized 1,4-difluoro-2,5-ditritiobenzene is characterized by the

specific activity of 54 ± 5 mCi μmol^{-1}, total activity of 788 ± 73 mCi, and tritium label multiplicity of 1.93 ± 0.18.

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REFERENCES

1. Nefedov, V.D., Sinotova, E.N., and Toropova, M.A., *Khimicheskie posledstviya β-raspada* (Chemical Consequences of β-Decay), Moscow: Atomizdat, 1978, pp. 126–179.
2. Nefedov, V.D., Sinotova, E.N., and Toropova, M.A., *Izv. Sib. Otdel. Akad. Nauk SSSR, Ser. Khim. Nauk*, 1980, no. 3, pp. 35–43.
3. Speranza, M., *Chem. Rev*., 1993, vol. 93, pp. 2933–2980.
4. Shchepina, N.E., Nefedov, V.D., Toropova, M.A., et al., *Tetrahedron Lett*., 2000, vol. 41, pp. 5303–5306.
5. Shchepina, N.E., Avrorin, V.V., Badun, G.A., et al., *Khim. Geterotsikl. Soedin.*, 2009, no. 7, pp. 1008–1014.
6. Shchepina, N.E., Avrorin, V.V., Badun, G.A., et al., *Vestn. Mosk. Gos. Univ., Ser. 2: Khim.*, 2009, vol. 50, no. 5, pp. 311–316.
7. Shchepina, N.E., Avrorin, V.V., Badun, G.A., et al., *Khim. Geterotsikl. Soedin.*, 2010, vol. 46, no. 5, pp. 692–698.
8. Shchepina, N.E., Avrorin, V.V., Aleksandrova, G.A., and Badun, G.A., *Perspekt. Mater.*, 2011, no. 10, pp. 339–344.
9. Gilchrist, T.L., *Heterocyclic Chemistry*, Harlow (UK): Longman, 1992, 2nd ed.
10. Pozharskii, A.F., Soldatenkov, A.T., and Katritzky, A.R., *Heterocycles in Life and Society*, New York: Wiley, 1997.
11. Joule, J.A. and Mills, K., *Heterocyclic Chemistry*, Blackwell Science, 2000, 4th ed.
12. *Chemistry of Organic Fluorine Compounds: II ACS Monograph 187*, Washington, DC, 1995.
13. Padeiskaya, E.N. and Yakovlev, V.P., *Ftorkhinolony* (Fluoroquinolines), Moscow: Bioinform, 1995.
14. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2005, 15th ed.
15. Wright, D.H., Brown, G.H., Peterson, M.L., and Rotschafer, J.C., *J. Antimicrob. Chemother*., 2000, vol. 46, pp. 669–683.
16. Noreddin, A.M., Haynes, V.L., and Zhanel, G.G., *J. Pharm. Pract*., 2005, vol. 18, pp. 432–443.
17. Melhus, A., *Expert Opin. Drug Saf*., 2005, vol. 4, pp. 299–309.
18. Murray, T.S. and Baltimore, R.S., *Pediatr. Ann*., 2007, vol. 36, pp. 336–342.
19. Boogaard, J., Kibiki, G.S., Kisanga, E.R., et al., *Antimicrob. Ag. Chemother*., 2009, vol. 53, pp. 849–862.
20. Talalaeva, T.V. and Kocheshkov, K.A., *Metody elementoorganicheskoi khimii (litii, natrii, kalii, rubidii, tsezii* (Methods of Organometallic Chemistry (Lithium, Sodium, Potassium, Rubidium, Cesium)), Moscow: Nauka, 1971, book 2, pp. 565–1192.
21. Shchepina, N.E., Avrorin, V.V., Badun, G.A., et al., *Radiokhimiya*, 2007, vol. 49, no. 6, pp. 551–553.