

# REARRANGEMENT OF SPIRODIOXOLANES UNDER THE ACTION OF THE VILSMEIER-HAACK REAGENT INTO FUNCTIONALIZED 4,5,6,7-TETRAHYDROBENZOFURANS

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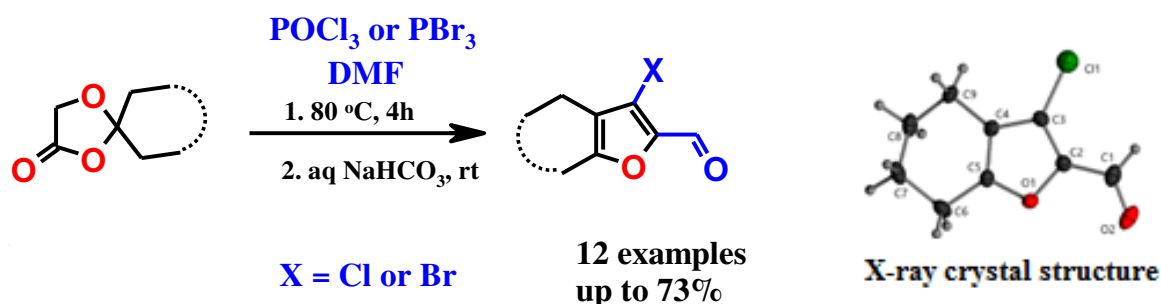
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Partially saturated heterocycles such as 4,5,6,7-tetrahydrobenzofurans are key components of many natural compounds, some of which have unique pharmacological activity. For example, atractylone has anti-apoptotic and antiviral activity, as well as anti-inflammatory and anti-hepatotoxic effects. Interestingly, the structurally related tubipofuran isolated from the Japanese stolonifer *Tubipora musica* Linnaeus is known as an ichthyotoxin against *Orizias latipes*. Another interesting representative of this class of compounds is isolinderactone. This substance has an antiproliferative and antimetastatic effect on cancer cells. The well-known menthofuran is the main toxin of spearmint, which is responsible for its lethal effects.

The heterocyclic moiety in benzofused systems can be selectively hydrogenated by catalytic hydrogenation and, as a result, there are many methods for the partial reduction of common benzofurans to 2,3-dihydrobenzofurans. However, complementary 4,5,6,7-tetrahydrobenzofurans, in which the benzene ring is partially saturated, are much more difficult to obtain.

During our work on the rearrangement of spiroimidazolines under the conditions of the Vilsmeier-Haack reaction, which leads to the formation of substituted pyridines [1], we realized that a related synthetic concept could open access to 4,5,6,7-tetrahydrobenzofurans, if used as starting compounds spirodioxolanes. The starting precursors are readily available from cyclic ketones, including 4-substituted cyclohexanones, which in turn are obtained from the corresponding phenols by reduction. Condensation of these ketones with glycolic acid readily converts them into the corresponding spirodioxolanes. As we expected, spirodioxolanes react with phosphorus oxychloride and DMF or phosphorus tribromide and DMF to form structurally complex 4,5,6,7-tetrahydrobenzofurans in high yields (Scheme 1).



Scheme 1. Rearrangement of spirodioxolanes under the action of the Vilsmeier-Haack reagent

The synthesized compounds are highly functionalized and can serve as low molecular weight building blocks for organic synthesis.

References:

1. O.K. Farat, N.V. Smetanin, S.A. Varenichenko, M.V. Kaidash, E.V. Zaliznaya, V.I. Markov. Novel rearrangement of substituted spiroimidazolidinones into quinoline derivatives *via* Vilsmeier-Haack reagent // *Tetrahedron Letters*. – 2021. – Vol 85. – P. 153464.