Thematic Section: Preparative Research. **Full Paper**
Subsection: Organic Chemistry.
The Reference Object Identifier – ROI: jbc-01/19-59-7-43
The Digital Object Identifier – DOI: 10.37952/ROI-jbc-01/19-59-7-43
Submitted on July 21, 2019.

One-step pilot method for obtain of substituted 3-benzyl-2-chloroquinolines from β-phenylpropaneamides using Vilsmeier-Haack reaction

© **Anton V. Omelkov**,[+] **Vadim I. Ilin**, **Mikhail B. Bodyagin**, **Yvsey A. Ruchko**, and **Vladimir E. Fedorov***
JSC «Pharm-Sintez». Entuziastov Ave., 38. Moscow, 105118. Russia.
E-mail: omelkov@mail.ru, Vfedorov@pharm-sintez.ru

*Supervising author; [+]Corresponding author

Keywords: Vilsmeier-Haack reaction, 3-benzyl-2-chloroquinolines, β-phenylpropaneamides, phosphoryl chloride, tuberculosis.

Abstract

The research for new substances among derivatives of phenylbutan-2-ols which have anti-tuberculosis activity against resistant forms of *Micobacterium Tuberculosis* led to the introduction of Bedaquiline (Sirturo®) into medical practice in 2014. Due to the completely new mechanism of action these substances in *M. tuberculosis*, this class has a great interest for search of new anti-TB drugs. Research in this area at JSC "*Pharm-Sintez*" allowed us to obtain new compounds such derivatives. One of them shows a good activity against drug-resistant Mycobacterium tuberculosis strains and can be produced in industry. Currently, the most promising derivatives (*R*,S*,S*,R**)-1-(6-bromo-2-chloro-3-quinolyl)-4-dimethylamino-2-(naphth-1-yl)-1-phenylbutan-2-ols undergo clinical trials and are under development for implementation in pilot production. In our chosen strategy for producing such alcohols, the key intermediate products are various substituted 3-benzyl-2-chloroquinolines.

The optimal method for synthesis of substituted 3-benzyl-2-chloroquinolines from different anilides was based on the Vilsmeier-Haak reaction. The purpose of our work was to determine all the conditions of the Vilsmeier reaction, affecting the yield of 2-chloroquinolines. The synthesis of the target compounds was made from 3-phenylpropanoic acid anilides and dimethylformamide (DMF) using phosphorus trichloride. 1,2-dichloroethane was originally used as a solvent and drying agent. The starting anilides of 3-phenylpropanoic acid are easily obtained using a modified Tang s method from corresponding anilines and 3-phenylpropanoic acid in good yields. Depending on the initial anilide, the optimization of the process parameters was carried out by temperature, time and solvent. Optimized conditions were used for a pilot production of 6-bromo-3-benzyl-2-chloroquinoline in a 200-liter reactor. The yields of the target products depend on the anilides and ranged between 65-82%.

References

[1] V. Baptiste, C. Crauste, M. Flipo et al. Tuberculosis: The drug development pipeline at a glance. *Eur. J. Med. Chem.* **2012**. Vol.51. P.1-16.
[2] A.V. Omelkov, V.F. Fedorov. The Effect of Lithium, Cerium(III), Copper(I) Chlorides on the Synthesis of 1-(2-Chloro-3-quinolyl)-4-dimethylamino-2-(1-naphtyl)-1-phenyl-butan-2-ols. *Book of abstracts, "2nd Russian Conference on Medicinal Chemistry", MedChem-2015. Novosibirsk.* **2015**. P.240.
[3] J. Guillemont, E. Pasquier, D. Lancois, Patent WO 2005075428 A1. Quinoline derivatives for use as mycobacterial inhibitors. *WIPO.* 18.08.**2005**.
[4] O. Meth-Cohn, S. Stanforth. The Vilsmeier-Haack Reaction. Comprehensive Organic Synthesis. Trost B.M. and Fleming I. (Editor-in-Chief), *Pergamon Press, Oxford, New York, Seoul, Tokyo.* **1991**. Vol.2. Chapter 3.5. P.777-794.
[5] A.V. Omelkov, V.I. Ilin, E.A. Ruchko, V.E. Fedorov. Industry method for substituted amides from anilines and 3-phenylpropionic acid. *Chemical Industry today.* **2013**. Vol.9. P.19-22. (russian)
[6] A.V. Omelkov, V.I. Ilin, E.A. Ruchko, V.E. Fedorov. One-step pilot method for obtain of substituted 3-benzyl-2-chloroquinolines from β-phenylpropaneamides using Vilsmeier-Haack reaction. *Chemical Industry today.* **2016**. Vol.11. P.27. (russian)