Synthesis of medchem-relevant Dimethylphosphine Oxide (DMPO) containing building blocks.

Y. Dmytriv, S. Ryabukhin, D. Volochnyuk, A.A. Tolmachev

Introduction and Aim

Despite wide abundance in the human body, phosphorus containing drugs generally considered as “exotic” class of medication including phosphonic or biphosphonic acid-based phosphate mimics, as well as several phosphonate, phosphinate, or phosphate-containing prodrugs. The main reasons of such considerations based on huge data about organophosphorus compounds toxicity and low bioavailability. It is leads to wide using of “organophosphorous cut-off filters” in majority of MedChem programs. But the recent development of Brigatinib (FDA approved at April 2017 as advanced ALK-positive metastatic non-small cell lung cancer) clearly showed that P=O bond in trisorganophosphin oxides could be used as a hydrogen-bond acceptor in kinase inhibitor design as well as introduction of P(O)Me2 moiety into the molecule could improve ADME properties.

This development initiated the program in our company directed to the design and synthesis the MedChem-relevant dimethylphosphine oxide (DMPO) containing building blocks. First the syntheses of two key intermediates, dimethylphosphine oxide 2 and dimethyl(phenyl)phosphine oxide 4, were optimized and scaled up to 1 kg from synthetic run in flow conditions. Compound 2 was further used in Pd-catalyzed cross-coupling reactions with functionalized (Het)aromatic halides meanwhile compound 4 was subjected to electrophilic substitution reactions. Combining these two approaches, as well as further functional group interconverting, leads to a set of DMPO-containing building blocks in multi-gram scale.

Synthesis of Some Examples

Results

Contacts

Dmitry M. Volochnyuk, Prof. Dr. Sci; Sergey V. Ryabukhin, Prof. Dr. Sci.
d.v.volochnyuk@gmail.com, s.v.ryabukhin@gmail.com.

Enamine Ltd, www.enamine.net 78 Chervonotkatska St, 02660 Kyiv, Ukraine