

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

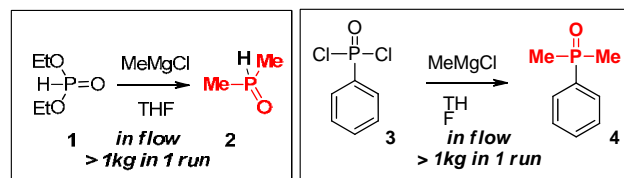
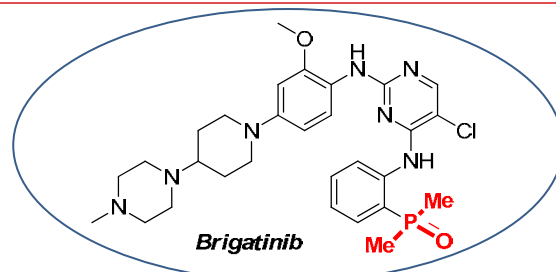
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## Introduction and Aim

Despite wide abundance in the human body, phosphorus containing drugs generally considered as "exotic" class of medication including phosphonic or bisphosphonic 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 leads to wide using of "organophosphorus 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 trisorganylphosphin oxides could be used as a hydrogen-bond acceptor in kinase inhibitor design as well as introduction of P(O)Me<sub>2</sub> moiety into the molecule could improve ADME properties.

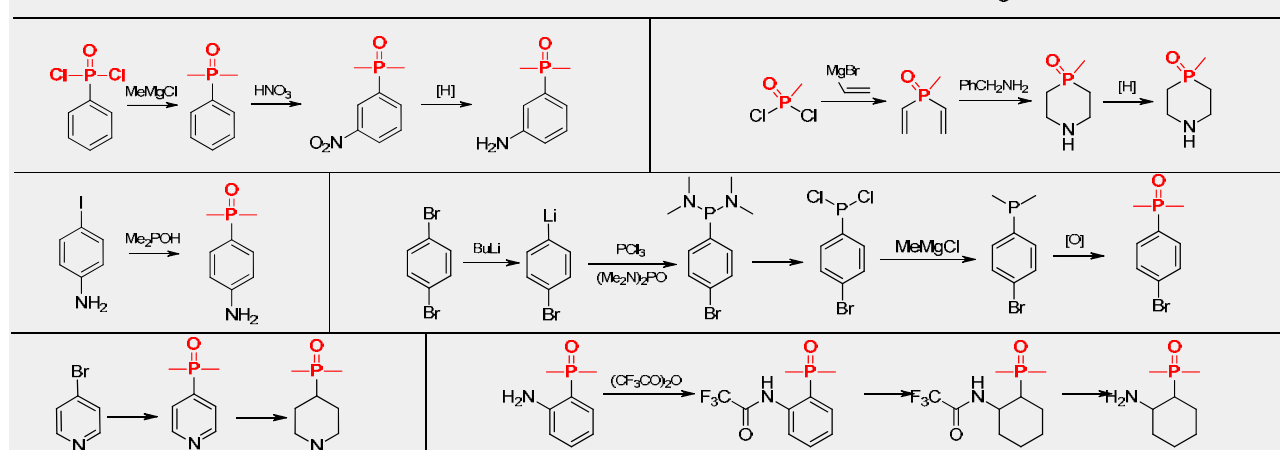
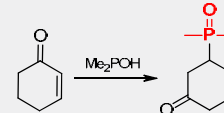
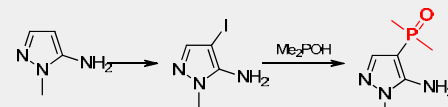
This development initiated the program in our company directed to the design and synthesis the MedChem-relevant dimethylphosphine oxide (DMPO) containing building blocks. First the synthesizes of two key intermediates, dimethylphosphine oxide **2** and dimethyl(phenyl)phosphine oxide **4**, were optimized 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

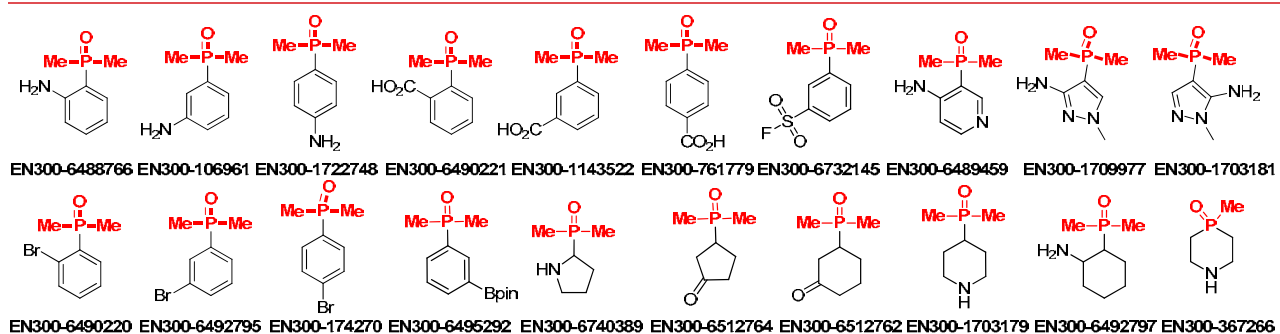


1. Pd-catalyzed cross-coupling  
2. Further functionalization

1. Electrophilic substitution  
2. Further functionalization



## Results



## Contacts

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