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Mendeleev Commun., 2018, **28**, 398–400

Mendeleev Communications

Synthesis and structure of new 2-aryl-substituted pyrrolidines containing phosphine oxide group

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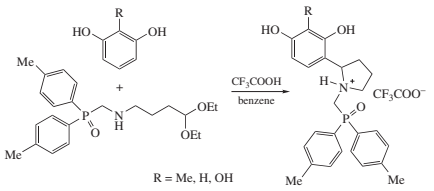
DOI: 10.1016/j.mencom.2018.07.019

2-Aryl-substituted pyrrolidines containing phosphine oxide group have been obtained by the reaction of *P*-(4,4-diethoxybutylaminomethyl)-*P*,*P*-di-*p*-tolylphosphine oxide with polyatomic phenols.



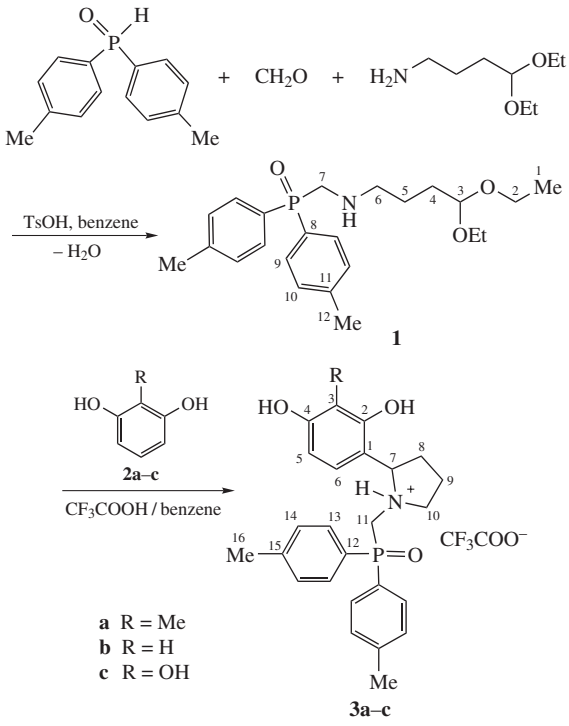
Pyrrolidine ring is included in many biologically active natural products,[1] alkaloids, and compounds that exhibit antitumor,[2] antibacterial,[3] antimicrobal,[4] neurotropic,[5] anti-inflammatory and anti-HIV activities.[6] The presence of a phosphonate group in biologically active molecules enhances their properties.[7] In this context, phosphorylated pyrrolidine derivatives can be of particular interest. Effective inhibitors of HIV protease and dipeptidyl peptidase IV,[8] thymidine phosphorylase,[9] purine nucleoside phosphorylase,[10] and 6-oxopurine phosphoribosyl transferase[11] were discovered among them.

Analysis of literature shows that effective syntheses of phosphorylated pyrrolidines are scarce in spite of their biological potential. The known methods mainly include: (i) direct electrophilic or nucleophilic phosphorylation of heterocyclic system;[12] (ii) ring closing of phosphoryl-functionalized substrates as a result of intramolecular cyclization, cycloaddition[13] and multi-component reactions.[14] Most of the methods relate to the preparation of 1-phosphonopyrrolidines or 2- or 3-phosphoryl substituted pyrrolidines. In spite of this positive background, simple and effective accesses to 2-aryl-substituted pyrrolidinylmethylphosphonates are lacking. At the same time, 2-aryl-substituted pyrrolidines are of interest as non-nucleoside HIV reverse transcriptase inhibitors (NNRTIs).[15] Incorporation of phosphonate moiety into compounds possessing NNRTI activity may improve their solubility and bioavailability.[16]

Assuming these facts, in the present work we aimed at developing novel synthesis of phosphorus-containing 2-aryl-substituted pyrrolidines. Recently, we obtained such compounds by acid-catalyzed intramolecular cyclization of *N*-(4,4-diethoxybutyl)ureas in the presence of phenols as nucleophiles.[17]

Here, the reaction of *P*-(4,4-diethoxybutylaminomethyl)-*P*,*P*-di-*p*-tolylphosphine oxide **1** with polyatomic phenols **2a–c** has been investigated for the first time in order to prepare phosphorylated 2-aryl-substituted pyrrolidines. Previously unknown amino acetal **1**† was synthesized by the reaction of 4,4-diethoxybutylamine with di-*p*-tolylphosphine oxide and paraformaldehyde in benzene in the presence of *p*-toluenesulfonic acid according to the Kabachnik–Fields reaction[18] (Scheme 1).

In the first experiments, amino acetal **1** reacted with 2-methylresorcinol **2a** in chloroform at room temperature in the presence of trifluoroacetic acid giving a hardly separable mixture of products. The MALDI mass spectra of the reaction mixture revealed the signals at *m*/*z* 560 $[M+H]^+$, corresponding to diarylbutylamine derivative, [4,4-bis(2,4-dihydroxy-3-methylphenyl)butylaminomethyl]di-*p*-tolylphosphine oxide, along with signal at *m*/*z* 435 $[M+H]^+$ of the target product **3a**. We have previously reported on the synthesis of diarylbutylamine derivative containing dihexylphosphorylmethyl group by the reaction of 2-methylresorcinol



Scheme 1

† P-*(4,4-Diethoxybutylaminomethyl)*-P,P-*di*-p-*tolylphosphine oxide* **1**. A mixture of di(*p*-tolyl)phosphine oxide (0.86 g, 3.74 mmol), 4,4-diethoxybutan-1-amine (0.6 g, 3.74 mmol), paraformaldehyde (0.11 g, 3.74 mmol) and TsOH (0.01 g) in benzene (50 ml) was heated under reflux in a flask equipped with a Dean–Stark trap for 6 h. When the