



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

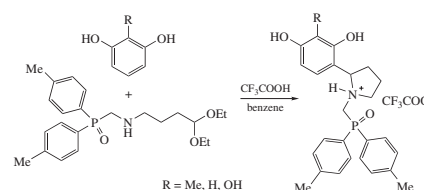
Liliya I. Vagapova,<sup>\*a</sup> Julia K. Voronina,<sup>a</sup> Victor V. Syakaev,<sup>a</sup> Alexander R. Burilov,<sup>a</sup>  
Airat R. Garifzyanov<sup>b</sup> and Mikhail A. Pudovik<sup>a</sup>

<sup>a</sup> A. E. Arbuзов Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of the Russian Academy of Sciences, 420088 Kazan, Russian Federation. Fax: +7 843 273 4872; e-mail: [vagapovan@mail.ru](mailto:vagapovan@mail.ru)

<sup>b</sup> Kazan Federal University, 420008 Kazan, Russian Federation

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

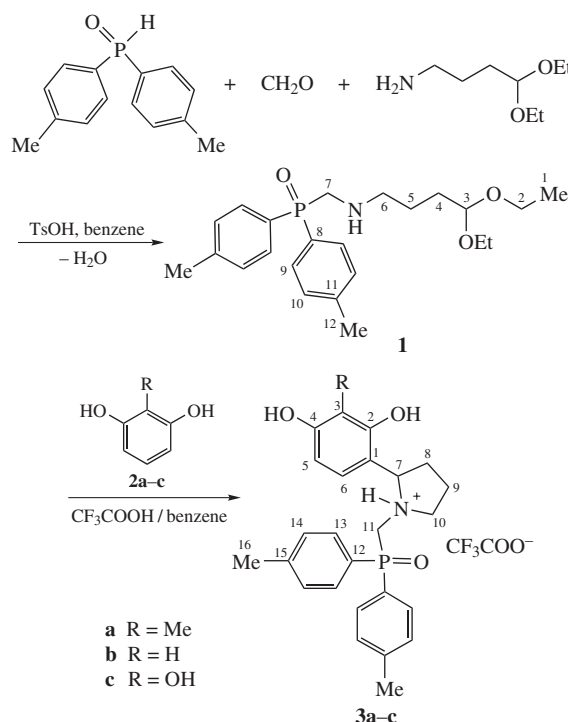
Analysis of literature shows that effective syntheses of phosphorylated pyrrolidines are scarce in spite of their biological potential. The known methods mainly include: (i) direct electrophilic or nucleophilic phosphorylation of heterocyclic system;<sup>12</sup> (ii) ring closing of phosphoryl-functionalized substrates as a result of intramolecular cyclization, cycloaddition<sup>13</sup> and multi-component reactions.<sup>14</sup> 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).<sup>15</sup> Incorporation of phosphonate moiety into compounds possessing NNRTI activity may improve their solubility and bioavailability.<sup>16</sup>

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.<sup>17</sup>

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**<sup>†</sup> was synthesized by the reaction of 4,4-diethoxy-

butylamine with di-*p*-tolylphosphine oxide and paraformaldehyde in benzene in the presence of *p*-toluenesulfonic acid according to the Kabachnik–Fields reaction<sup>18</sup> (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]<sup>+</sup>, 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]<sup>+</sup> of the target product **3a**. We have previously reported on the synthesis of diarylbutylamine derivative containing dihexylphosphorylmethyl group by the reaction of 2-methylresorcinol



**a** R = Me  
**b** R = H  
**c** R = OH

Scheme 1

<sup>†</sup> *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