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LETTERS TO THE EDITOR

Dedicated to V. F. Mironov on His 60th Anniversary

Reactions of Vinylphosphonates with Piperazines

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Abstract—Dialkyl [2-(piperazin-1-yl)ethyl]phosphonates were obtained by the reactions of piperazine with dialkyl vinylphosphonates. The addition of 2-(piperazin-1-yl)ethanamine to diethyl vinylphosphonate involves the primary exocyclic amino group of the heterocyclic compound.

Keywords: vinylphosphonates, piperazine, 2-(piperazin-1-yl)ethanamine

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Phosphorylation of pharmacophoric nitrogen heterocycles can extend the range of their biological activity [1, 2]. We have studied the reaction of diethyl vinylphosphonate **1** with piperazine **2**. Heating an equimolar mixture of compounds **1** and **2** at 80°C in anhydrous ethanol for 2 h gave diethyl [2-(piperazin-1-yl)ethyl]-phosphonate **3** in 78% yield (Scheme 1). The structure of compound **3** was established by IR and ^{1}H and ^{31}P NMR spectroscopy. The IR spectrum **3** displays a band at 3200–3300 cm^{-1} assignable to the stretching vibrations of the NH group and a strong band at 1245 cm^{-1} (P=O), and does not contain a C=C absorption band (1640 cm^{-1}). The ^{31}P NMR spectrum contains a single signal at δ_P 31.3 ppm, which suggests the formation of a single adduct.

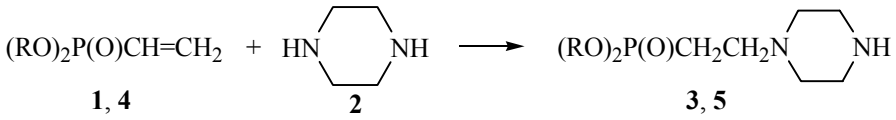
Under the same conditions, by reacting diisopropyl vinylphosphonate **4** with piperazine **2** we obtained diisopropyl [2-(piperazin-1-yl)ethyl]phosphonate **5** in 71% yield (Scheme 1).

The reaction of vinylphosphonate **1** with 2-(piperazin-1-yl)ethanamine **6** at a 1 : 1 reagent ratio can involve the exocyclic NH group of compound **6** (Scheme 2, route *a*) and/or the NH group of the piperazine ring (route *b*). A mixture of compounds **1** and **6** was heated in anhydrous ethanol at 80°C until the IR spectrum of the mixture no longer displayed the C=C stretching vibration band at 1640 cm^{-1}. The ^{31}P NMR spectrum showed a single signal at δ_P 31.1 ppm.

The semiempirical quantum-chemical method PM3 was used to calculate standard Gibbs energies of optimized reagent molecules **1** and **6** and suggested products of their reaction **7** and **8.** The ΔG^0 values for the reaction routes *a* and *b* were estimated by conventional thermodynamic calculations [3]. The ΔG^0 for the reaction leading to product **7** (route *a*) was –11.29 kJ/mol, and the ΔG^0 for the reaction leading to product **8** (route *b*) was –10.76 kJ/mol. It was thus concluded that route *a* leading to adduct **7** is a thermodynamically preferred reaction route.

Taking into account the ^{1}H and ^{31}P NMR data and the results of quantum-chemical calculations we consider it safe to state that the reaction of vinylphosphonate **1** with 2-(piperazin-1-yl)ethanamine **6** involves the primary amino group of the nucleophilic reagent (route *a*) and

Scheme 1.



1, **4** **2** **3**, **5**

R = Et (**1**, **3**); *i*-Pr (**4**, **5**).