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Synthesis and Characterization of New 1*H*-pyrazolo[3,4-*b*]pyridine Phosphoramidate Derivatives

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Abstract: *Twelve new 1H-pyrazolo[3,4-b]pyridine phosphoramidate derivatives were synthesized under mild conditions by nucleophilic aromatic substitution reaction of inoalkylphosphoramidates over 4-Cl substituted pyrazolo[3,4-b]pyridine in good yields. The new compounds were characterized by IR, 1H, 13C and 31P NMR spectroscopy and HRMS. The crystal structure of one compound was solved by X-ray diffraction and showed a network of intermolecular interactions involving phosphoramidate groups.*

Keywords: *1H-Pyrazolo[3,4-b]pyridine, crystal structure, phosphoramidate, pyrazolopyridines*

1. INTRODUCTION

Fused heterocyclic containing pyrazolopyridine systems have been described associated with several biological and medicinal activities.1-4 Substituted pyrazolo[3,4-*b*]pyridines represent a very important building block in organic synthesis and numerous studies have been reported due to their well-documented biological activity.5-8 Several 4-substituted pyrazolo[3,4-*b*]pyridines have been obtained by our group through nucleophilic substitution of the 4-chloro precursor with variable nucleophiles and showed antileishmanial,5 antiviral9 and antibacterial10,11 promise.It is known that coupling molecules with well-established pharmacological activities might be a good strategy to develop new significant products.12 In this context, heterocyclic linked to other biologically active molecules, like, *e.g*., phosphoramidates, can give rise to new derivatives with potential biological applications.13-18 Introduction of a phosphoramidate group essentially changes the physical and chemical properties of the parent molecule, resulting in the improvement of both polarization and intermolecular bonding characteristics.19,20 Our particular interest in the synthesis of substituted 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates is use them in chemotherapies for tropical diseases. In this work we report the first synthesis of pyrazolopyridine phosphoramidate derivatives as well as a discussion based on the X-ray diffraction of one representative derivative

2. RESULTS AND DISCUSSION

The syntheses of the new 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates **8a-l** were performed by nucleophilic aromatic substitution of the chlorine atom in 4-substituted pyrazolo[3,4-*b*]pyridines (**4a-c**) by aminoalkylphosphoramidates **7a-d** (Scheme 1). The starting 4-chloro-1*H*-pyrazolo- [3,4-*b*]pyridine derivatives **4a-c** were available in our laboratory and could be easily prepared from condensation of appropriate hydrazine (**1a,b**) and _-aminocrotononitrile or benzoylacetonitrile, followed by condensation of the intermediate 5-aminopyrazoles (**2a-c**) with diethyl ethoxymethylenemalonate and then by 'chlorocyclization' with POCl3. Finally **4a-c** were purified by recrystallization from ethanol.21-24 Nucleophilic aromatic substitution of the chlorine atom in 4-substituted pyrazolo[3,4-*b*]- pyridines by amines has been used as a versatile route to new pyrazolopyridine derivatives.5,9,27-30 Thus, reaction of **4a-c** with an excess (2 equiv.) of aminoalkylphosphoramidates **7a-d** in refluxing THF for 9 to 12 h afforded the 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates derivatives **8a-l** in 52-98% yield (Table 1). The presence of an electronwithdrawing group (-CO2Et) in 5-position of the substrate **4** and the excess of the nucleophilic agent **7** facilitate the reaction. The products were fully characterized by infrared, 1H, 13C, and 31PThe 1H NMR spectra of compounds **8a-l** showed a singlet in the range of 8.85-9.00 ppm attributable to the pyridine ring proton. The same spectra showed a quartet and triplet signals related to the ethyl ester group in the ranges 4.27-4.38 ppm and 1.38-1.41 ppm, respectively. The resonances of the isopropyl protons appeared as two doublets at 1.17-1.32 ppm and a doublet of septets around 4.56 ppm with 3 *J*HH ~ 6.2 Hz and 3 *J*PH ~ 7.5 Hz. The NH signal was detected as a broad triplet in the range 8.76-9.31 ppm with 3 *J*HH ~ 5.1 Hz . On the other hand, NHP protons showed coupling with phosphorus and the neighbor methylene group, giving rise to a doublet of triplet around 2.80 ppm with 3 *J*HH ~ 7.0 Hz and 2H ~ 9.0 Hz. In the aliphatic region, theunequivocal assignment of the signals for methylene protons was based on COSY correlations.The *N*-

methyl protons signal of compounds **8a-d** appeared as a singlet around 2.65-3.98 ppm and NMR spectroscopies and by high resolution mass spectrometry (HRMS).Single crystals of compound **8j** suitable for X-ray diffraction were obtained by slow solvent evaporation at room temperature. The crystal data and structure refinement parameters for this compound are provided (See Supplementary Material, Table S1). The ORTEP representation of the asymmetric unit is shown in Figure 1. In this structure, the phosphoramidate group nitrogen atom is bonded to an aliphatic chain containing three carbon atoms, namely C1, C2 and C3. The bond lengths and angles are typical of phosphoramidate groups (Table S2). The 5- as also observed. Furthermore, dimers of molecules raised due to the intermolecular hydrogen bonding involving the phosphoramidate O1 and N1 atoms (Figure 2), as previously reported for this compound class

3. CONCLUSIONS

The methodology for nucleophilic aromatic substitution of the chlorine atom in 4-substituted pyrazolo[3,4-*b*]pyridine was successfully applied to aminoalkylphosphoramidates as the nucleophile. In this context, twelve new reported 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates were synthesized and characterized. The crystal data for a representative compound pointed out the formation of dimer due to the intermolecular hydrogen bonding involving the phosphoramidate O and N atoms.

Experimental Section

General. Analytical grade reagents and solvents were purchased from commercial sources and used without further purification. Melting points were obtained with a Fisher-Johns apparatus. 1H, 13C and 31P NMR spectra were recorded on a Varian UP-300 spectrometer at 299.95, 75.42 and 121.42 MHz, respectively, with TMS as internal standard or 85% H3PO4 as external standard. The chemical shifts (□) are reported in ppm and the coupling constants (*J*) in hertz.TLC was carried out using silica gel F-254 Glass Plate (20 × 20 cm). Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. High resolution mass spectra (EI-70eV) were performed on a Varian MAT CH7 8500 direct inlet instrument. The Clsubstituted pyrazolo[3,4-*b*]pyridine (**4a-c**)21-24 and aminoalkylphosphoramidates compounds were prepared as previously reported.

Typical procedure for preparation of 1*H*-pyrazolo[3,4-*b*]pyridine phosphoramidates derivatives (8a-l).

Cl-substituted pyrazolo[3,4-*b*]pyridine (**4a-c**) (2.2 mmol) and the aminoalkylphosphoramidate (**7a-d**) (4.4 mmol) were dissolved in THF (10 mL) and the reaction mixture was heated at reflux until the disappearance of the starting **4** (9-12 h, monitored by TLC). The mixture was poured into ice and the resulting solid (except **8d,i,k,l**) was filtered off,washed with distilled water and dried. Solids were recrystallized from ethanol/water (1:3).Compounds **8d,i,k,l** were diluted with chloroform and washed with water (3 × 10 mL). The organic layer was dried with anhydrous sodium sulfate and filtered, and the solvent was evaporated under reduced pressure giving an oily product.

Diisopropyl2-[5-(ethoxycarbonyl)-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-ethylphosphoramidate (8a).

Pale brown solid; yield 80%; mp 125-126 °C; IR (KBr, _max, cm-1):3222 (m, N-H), 2978 (m), 2933 (m), 1671(s, C=O), 1586 (s), 1538 (m), 1434 (m), 1372 (w),1339 (m), 1269 (m,P=O), 1188 (m), 1108 (m), 978 (s, P-O), 899 (w), 795 (w), 665 (w); 1H NMR (CDCl3): _H 1.25 and 1.28 (2d, 12H, 3*J*(HH) 6.4), 1.40 (t, 3H, 3 *J*(HH) 6.9), 2.66 (s, 3H), 2.85 (dt, 1H, 3 *J*(HH) 5.4 and 3.6), 3.28 (m, 2H), 3.74 (dt, 2H, 3 *J*(HH) 6.0 and 5.4), 3.98 (s, 3H), 4.34 (q,2H, 3 *J*(HH) 6.9), 4.57 (dsep, 2H, 3 *J*(HH) 6.3 and 3 *J*(PH) 7.5), 8.86 (s, 1H), 9.24 (br t, 1H, 3 *J*(HH) 5.0); 13C NMR (CDCl3): _C 14.16, 18.44, 23.61 (d, 3 *J*(PC) 5.1), 33.55, 41.83, 49.69 (d, 2 *J*(PC) 5.9),60.41, 70.94 (d, 2 *J*(PC) 5.9), 100.61, 103.08, 140.19, 152.33, 154.13, 154.93, 169.24; 31P NMR (CDCl3): _P 7.18 (s); HRMS (EI): *m*/*z* [M+H] calcd. for C19H32N5O5P: 441.21411. Found:441.21400.

Diisopropyl3-[5-(ethoxycarbonyl)-1,3-dimethyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-ylamino]-propylphosphoramidate (8b).

Pale brown solid; yield 60%; mp 118-120 °C; IR (KBr, _max, cm-1): 3213 (m, N-H), 2976 (m), 2933 (m), 1663(s, C=O), 1583 (s), 1536 (m), 1457 (m), 1372 (w), 1337 (m), 1264 (m, P=O), 1228 (m), 1185 (m), 1115 (m), 978 (s, P-O), 897 (w), 800 (w),658 (w); 1H NMR (CDCl3): _H 1.27 and 1.29 (2d, 12H, 3 *J*(HH) 6.0), 1.38 (t, 3H, 3*J*(HH) 7.2), 1.94 (quin, 2H, 3 *J*(HH) 6.6), 2.54 (dt, 1H, 3 *J*(HH) 8.7 and 7.2), 2.67 (s, 3H), 3.06 (m, 2H), 3.69 (dt, 2H,3

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