Synthesis of New Imidazo [1,2-a] Pyridine and their NMR Spectral Data

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This paper describes synthesis of new imidazo[1,2-a] pyridine derivatives. The products structures were confirmed by elemental analysis, ^{1}H-NMR, and ^{13}C-NMR.

Keywords: imidazo[1,2-a]pyridines, condensations, NMR

Imidazo-pyridine derivatives are well known for their important biological properties: antiallergic activity [1-2], antituberculosis effects [2], anti-inflammatory action [3,4], and antihypertensive effects [5,6].

Experimental part

Material and equipment

All used reagents are Aldrich commercial products.

Elemental analyses were effectuated on a Carlo Erba 1106 analyser.

^{1}H-NMR spectra were run on a BRUKER ARX 400 spectrometer at 400 MHz, in $CDCl_3$ solution, using TMS as internal standard.

^{13}C-NMR spectra were recorded on a BRUKER ARX 400 spectrometer at 100 MHz, in $CDCl_3$ solution, using TMS as internal standard.

Melting points were measured with the help of a Boëtius apparatus.

Methods

p-methyl-ω-bromoacetophenone synthesis

To a two-necked round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser, a dropping funnel, a drying tube and 400 mL of acetic acid, were added 1 mol of 4-methylacetophenone and 1 mol of bromine. The resulting mixture was stirred at room-temperature for 5h. Acetic acid was distilled under vacuum (temperature bellow 45°C). The solid residue was purified by recrystallization from ethanol and dried under reduced pressure for 24 h. Yield, 60%. Melting point 50.5°C. Elemental analysis: molecular formula C_9H_9BrO, %C(calculated/found)= 50.70/50.67, %H(calculated / found)=4.22/4.20.

4-clorometil-w-bromoacetophenone synthesis

1) p-chloromethylbenzoyl chloride preparation: a sample of 0.2 mol of p-chloromethylbenzoic acid and 0.4 mol of thionyl chloride in 300 mL of cyclohexane was refluxed for 8.5h. When the reaction was complete, the cyclohexane was removed under reduced pressure and the solid residue was recrystallized from petroleum ether. Yield 79%. Melting point 31°C. Elemental analysis: molecular formula $C_8H_6Cl_2O$, %C(calculated/found)=50.79/ 50.73, %H(calculated/found)= 3.17/3.15.

2) (p-diazoacetyl)benzyl chloride preparation: in a cold petroleum ether solution containing 30 mL of triethylamine and 0.18 mol of diazomethane (diazomethane is easily generated [9] pouring an aqueous solution of NaOH on Diazald - 0.28 mol of N-methyl-N-nitroso-p-toluenesulphonamide) was quickly added 0.15 mol of p-(chloromethyl)benzoyl chloride. The resulting mixture was stirred for 2.5 h, then, the solvent was evaporated. The remaining residue was washed twice with water and the heterogeneous mixture was extracted with chloroform. Chloroform was removed by distillation and a pure product resulted. Yield 99%. Product melting point 88°C. Elemental analysis: molecular formula $C_7H_7N_2ClO$, %C(calculated/ found)=49.26/49.23, %H(calculated/found)=4.10/4.08.

3) 4-chloromethyl-ω-bromoacetophenone preparation: 0.1 mol of (p-diazoacetyl)benzyl chloride was dissolved in 400 mL of chloroform, afterwards, 25 mL of 45% hydrobromic acid and 250 mL of water were poured. The mixture was stirred for 1 h, and then the solvent was evaporated (temperature below 45°C). A pure solid product resulted, yield 99%. Melting point 85°C. Elemental analysis: molecular formula C_9H_8ClBrO, %C(calculated/found)= 43.63/43.57, %H (calculated/found)= 3.23/3.19.

A) *2-(p-methylphenyl) imidazo[1,2-a]pyridine synthesis* (Compound N° 1).

To 50 mL of acetonitrile was dissolved 0.05 mol of *p*-methyl-ω-bromoacetophenone. Afterwards, a solution of 0.05 mol of 2-aminopyridine in 110 mL of acetonitrile was added dropwise with the help of a reparatory funnel. Mixture was stirred at room-temperature for 2h, afterwards was refluxed for 11h. The acetonitrile was evaporated. The resulting solid bromide salt was dissolved in water, neutralized with potassium carbonate and extracted with chloroform. The chloroform layer was separated and dried over anhydrous Na_2SO_4. Sodium sulphate was filtered off and then the solvent was evaporated from filtrate. The resulting crude product was purified by recrystallization from ethylic alcohol and, finally, dried. The yield and product properties are shown in table 1.

B) *2-(p-methylphenyl) imidazo-3-bromo[1,2-a]pyridine synthesis* (Compound N° 2).

0.05 mol of 2-(p-methylphenyl)imidazo[1,2-a]pyridine was dissolved in 100 mL of warm CCl_4. 0.055 mol of Nbromosuccinimide and 1 g of benzoyl peroxide were added and the mixture was refluxed for 12h. The resulting mixture was filtered, the filtrate was evaporated and the solid residue was recrystallized from ethanol and dried. The yield and product properties are shown in table 1.

C) *2-(p-(chloromethyl)phenyl) imidazo[1,2-a]pyridine synthesis* (Compound N° 3).

To 300 mL of acetonitrile was dissolved 0.2 mol of 2-aminopyridine and a solution of 0.2 mol of 4-clorometil-ω-bromoacetophenone in 200 mL of acetonitrile. The

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resulting solution was stirred for 10 h, and then the obtained precipitate was filtered off. The precipitate was dissolved in 350 mL of ethanol and refluxed for 3.5h. The ethanol was removed under vacuum, afterwards the obtained residue was dissolved in 300 mL of water and neutralized with sodium bicarbonate until *p*H=8. The mixture was extracted with 300 mL of chloroform and the chloroform layer was dried over magnesium sulphate. The magnesium sulphate was filtered off, and the solvent was removed from the filtrate by evaporation. Solid residue was purified by recrystallization from ethyl acetate and dried. The synthesis yield and product properties are exhibited in table 1.

D) *Diethyl 4-[(2-imidazo[1,2-a] pyridyl] benzyl] fosfonate synthesis* (Compound N° 4).

A sample of 0.03 mol of 2-(p-(chloromethyl)phenyl) imidazo[1,2-a]pyridine and 0.037 mol of triethyl phosphite was refluxed at 155°C for 6h. Non-reacted triethyl phosphite was removed by distillation under reduced pressure. The resulting residue was purified by recrystallisation form ethyl acetate. The physical properties of the product and the yield of the synthesis are shown in table 1.

Results and discussion

Several new derivatives of imidazo[1,2-a]pyridine were synthesised from 2-aminopyridine by condensation and substitution reactions. The product synthesis was effectuated by the following reactions.

The physical properties of the new obtained products and the yields of the synthesis are shown in the table 1. Chemical shifts and coupling constants measured from NMR spectra are indicated in table 2.

The chemical structures of the products were attributed by ^{1}H- and ^{13}C-NMR analysis. Identification of magnetic equivalent nucleus and the ^{1}H-NMR coupling constants were also done. The protons H_2, H_6 exhibit the same chemical shifts. The nucleus H_3, H_5 are also equivalent.

The substituent type, X(H and Br) and Z, induces chemical shifts alterations of the benzenic and pyridinic protons. The vicinal protons of the pyridinic skeleton show an ortho strong coupling: $J_{5'6'}$=7.5-7.8 Hz, $J_{6'7'}$=6.6-6.7 Hz, $J_{7'8'}$=7.1-8.1Hz. The meta coupling of the same nucleus are rather poor in the agreement with literature data of the analogous compounds [7]. Generally, the substituent X and Z don't change considerably the constants values (Table 1). The only one nucleus, whose absorption signal is less modified by various nucleus environments, is proton H_3. In the case of diethyl 4-[(2-imidazo[1,2-a] pyridyl] benzylphosphonate we found out a strong coupling interaction between the two methylenic protons and the neighbouring phosphorous atom ^{2}J=21.7Hz.

The absorption peaks of the non-equivalent carbon atoms are easily hit in the ^{13}C-NMR spectra.

The ^{13}C-chemical shifts depend strongly on the atom hybridization and carbon type: primary, secondary, tertiary and quaternary [7,8]. The substituents on the carbon atom

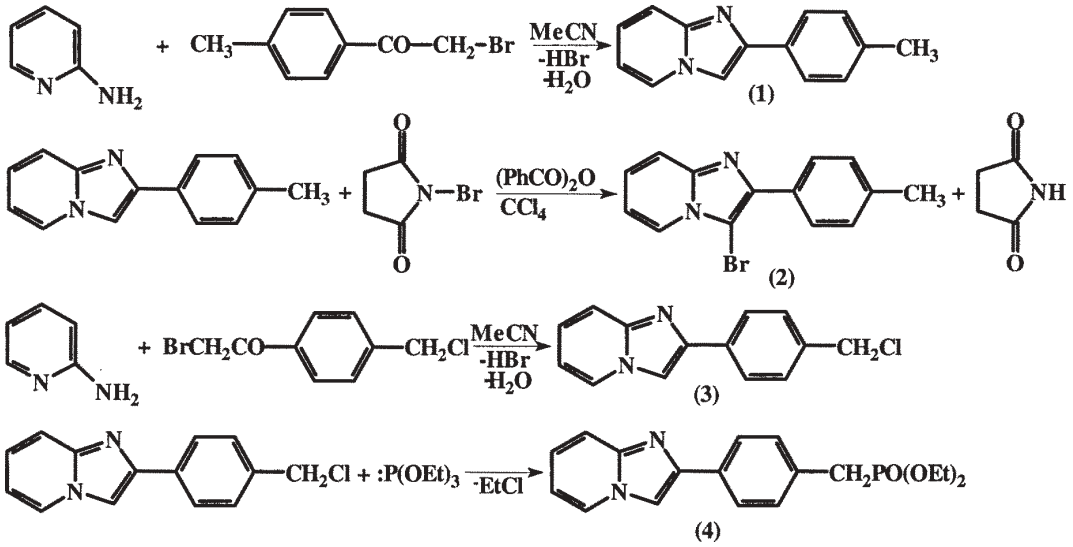


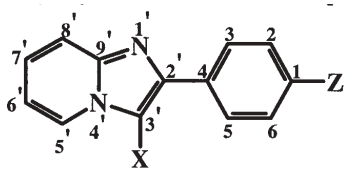
Table 1
IMIDAZO [1,2-A] PYRIDINE DERIVATIVES

N° Comp.	Molecular formula	Elementary analysis calculated / found %C	%H	%N	mp[°C]	Yield [%]
1	$C_{14}H_{12}N_2$	80.76	5.76	13.46	147.5	80
		80.71	5.73	13.43		
2	$C_{14}H_{11}BrN_2$	58.53	3.83	9.75	119	75
		58.47	3.79	9.72		
3	$C_{14}H_{11}ClN_2$	69.27	4.53	11.54	255	73
		69.23	4.51	11.52		
4	$C_{18}H_{21}N_2O_3P$	62.79	6.10	8.13	110	62
		62.76	6.04	8.11		

Obs.: mp- melting point

Table 2

CHEMICAL SHIFTS AND COUPLING CONSTANTS FROM NMR SPECTRA OF THE COMPOUNDS



Comp.	^{1}H – NMR δ[ppm], J[Hz]	^{13}C - NMR δ[ppm]
1	2.36(s,3H,$\underline{CH_3}$) ;6.64(m,1H,$H_{6'}$,$J_{6'5'}$=7.5, $J_{6'7'}$=6.6, $J_{6'8'}$=1.2) ;7.05(m, 1H, $H_{7'}$, $J_{7'8'}$=7.1, $J_{7'6'}$=6.6, $J_{7'5'}$=1.1) ;7.19 (d,2H,H_2,H_6, J_{23}=8) ; 7.56(m,1H,$H_{8'}$, $J_{8'7'}$=7.1, $J_{8'6'}$=1.2) ; 7.63(s,1H,$H_{3'}$) ;7.80(d,2H,H_3,H_5,J_{32}=8); 7.94(m,1H,$H_{5'}$, $J_{5'6'}$=7.5, $J_{5'7'}$=1.1)	21.22($\underline{C}H_3$) ;107.70($C_{3'}$) ;112.25($C_{6'}$) ; 117.28($C_{8'}$) ;124.47($C_{7'}$) ;125.43($C_{5'}$) ; 125.85(C_3) ;129.35(C_2) ;130.75(C_1) ; 137.74(C_4) ;145.48($C_{2'}$) ;145.70($C_{9'}$)
2	2.39(s,3H,$\underline{CH_3}$) ; 6.81(m, 1H, $H_{6'}$, $J_{6'5'}$= 7.6, $J_{6'7'}$=6.7, $J_{6'8'}$=1.3) ; 7.16(m,1H,$H_{7'}$, $J_{7'8'}$=7.6, $J_{7'6'}$=6.7, $J_{7'5'}$=1.2) ; 7.27(d,2H,H_2,H_6,J_{23}=7.9) ;7.60(m,1H,$H_{8'}$, $J_{8'7'}$=7.6, $J_{8'6'}$=1.3); 8.05(d, 2H, H_3, H_5, J_{32}=7.9) ; 8.08(m, 1H, $H_{5'}$, $J_{5'6'}$=7.6, $J_{5'7'}$=1.2)	21.20(CH_3) ;91.30($C_{3'}$) ;112.83($C_{6'}$) ; 117.29($C_{8'}$) ;123.73($C_{7'}$) ;124.85($C_{5'}$) ; 127.24(C_3) ;129.01(C_2) ;129.69(C_1) ; 138.08(C_4) ;142.50($C_{2'}$) ;145.18($C_{9'}$)
3	4.61(s,2H,$\underline{CH_2}$) ; 6.79 (m, 1H, $H_{6'}$, $J_{6'5'}$= 7.7, $J_{6'7'}$=6.6, $J_{6'8'}$=0.9); 7.19(m,1H,$H_{7'}$, $J_{7'8'}$=7.4, $J_{7'6'}$=6.6, $J_{7'5'}$=0.9) ; 7.45(d,2H,H_2,H_6,J_{23}=8.4) ;7.64(m,1H,$H_{8'}$, $J_{8'7'}$=7.4, $J_{8'6'}$=0.9) ; 7.89(s,1H,$H_{3'}$) ; 7.91(d,2H,H_3,H_5,J_{32}=8.4) ; 8.14(m,1H,$H_{5'}$, $J_{5'6'}$=7.7, $J_{5'7'}$=0.9)	46.21($\underline{C}H_2$) ;106.98($C_{3'}$) ;112.20($C_{6'}$) ; 117.31($C_{8'}$) ;124.53($C_{7'}$) ;125.37($C_{5'}$) ; 126.02(C_3) ;129.31(C_2) ;130.12(C_1) ; 137.75(C_4) ;145.52($C_{2'}$) ;145.72($C_{9'}$)
4	1.22(t, 6H, CH_2-$\underline{CH_3}$, J_{CH3CH2}=7.2) ; 3.20(d, 2H, P-$\underline{CH_2}$, J_{CH2P}=21.7) ; 4.03(m,4H,CH_3-$\underline{CH_2}$, J_{CH2CH3}=7.2) ; 6.76 (m, 1H, $H_{6'}$, $J_{6'5'}$=7.8, $J_{6'7'}$=6.7, $J_{6'8'}$=1.1) ; 7.14(m, 1H,$H_{7'}$, $J_{7'8'}$=8.1, $J_{7'6'}$=6.7, $J_{7'5'}$=0.8) ; 7.38(d,2H,H_2,H_6, J_{23}=8.3) ; 7.61 (d, 1H, $H_{8'}$, $J_{8'7'}$=8.1, $J_{8'6'}$=1.1) ; 7.84(s,1H,$H_{3'}$) ;7.91(d,2H,H_3,H_5,J_{32}=8.3,) ; 8.12(m,1H,$H_{5'}$, $J_{5'6'}$=7.8, $J_{5'7'}$=0.8)	16.36(CH_3) ;32.58(P-$\underline{C}$) ;62.27(CH_3-$\underline{C}H_2$) ; 108.06($C_{3'}$) ;112.38($C_{6'}$) ;117.38($C_{8'}$) ; 124.77($C_{7'}$) ;125.56($C_{5'}$) ;126.02(C_3) ; 129.88(C_2) ;131.02(C_1) ;132.16(C_4) ; 145.3($C_{2'}$) ;145.65($C_{9'}$)

shift the signal more downfield as compared to the corresponding shift in proton spectra. On the pyridinic skeleton where no substituent is present the ^{13}C-peaks positions don't suffer important variation (table 1).

All ^{13}C-chemical shifts are in agreement with those of the similar products [8].

Conclusion

Four new derivatives of imidazo [1,2-a] pyridine were synthesised and characterized by ^{1}H- and ^{13}C-NMR spectroscopy, elemental analysis and melting points. The yields of the synthesis vary in the range 60% to 80%.

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