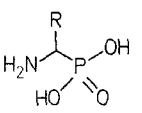

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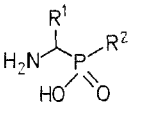
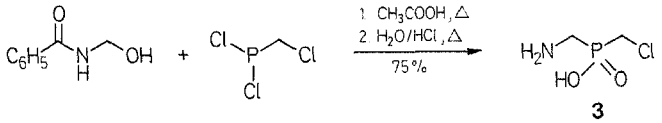


2

We now report the synthesis of a series of (chloromethyl)phosphinic analogs of amino acids (3 and 4), which are of interest as intermediates for the functionalization of the chloromethyl group. Our approach involves the use of the amidoalkylation reaction of phosphorus trichloride and its organic derivatives.[6-8] This proposed reaction presents a special advantage, since other synthetic methods require the use of amines, which can react with the P-CH_2Cl group.

1-Aminomethyl(chloromethyl)phosphinic acid (3) was obtained by amidoalkylation of dichloro(chloromethyl)phosphine in acetic acid solution with *N*-hydroxymethylbenzamide; 1-aminoalkyl(chloromethyl)phosphinic acids **4** were obtained by amidoalkylation of dichloro(chloromethyl)phosphine with benzyl carbamate and suitable aldehydes (Table 1).



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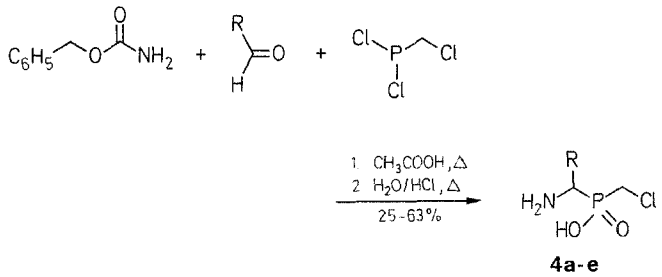
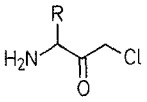
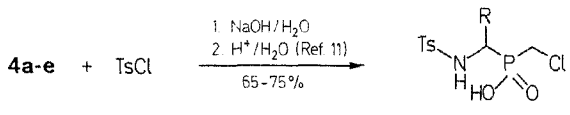


4a-e



5

Compounds **4** show formal similarity with the chloromethylketones **5**. Considering the irreversible inactivation of some proteolytic enzymes by *N*-tosyl derivatives of **5**,[9,10] we have prepared the tosylated compounds **6** (Table 2) and examined their interaction with trypsin and chymotrypsin.



Ts = *p*-toluenesulfonyl

6a-e

No inhibition of trypsin and chymotrypsin was observed, however, even upon prolonged incubation with to up 0.01 molar solution of any of the compounds **6**. This result could be due to the known low reactivity of the P-CH_2Cl function towards nucleophiles.

IR spectra were determined on Perkin-Elmer spectrophotometer. ^1H NMR spectra were recorded on a Tesla 100 MHz spectrometer. Elemental analyses were performed by Central Laboratory in Institute of Organic and Physical Chemistry, Technical University of Wrocław.

1-Aminoalkyl(chloromethyl)phosphinic Acids and Their *N*-Tosyl Derivatives

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A series of 1-aminoalkyl(chloromethyl)phosphinic acids **3** and **4** were synthesized in good yields. These compounds are of interest as intermediates for functionalization of the CH_2Cl group.

The biological activity of 1-aminoalkylphosphonic acids **1** is well documented.[1-4] In contrast, only a few examples of phosphinic acids **2**, where the R^2 moiety = methyl, ethyl, or phenyl, are known.[5]

Table 1. 1-Aminoalkyl(chloromethyl)phosphinic Acids **3** and **4**

Product	R	Yield (%)	m.p. (°C)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (solvent, HMDSO$_{ext}$) δ (ppm)
3	H	75	208–209	$C_2H_7ClNO_2P$ (143.5)	3400–3300, 2800–2500, 1600, 1400, 1200	(D_2O): 3.91–3.83 (d, 4H, J_{HP} = 14 Hz, CH_2PCH_2)
4a	CH_3	55	207–208	$C_3H_9ClNO_2P$ (157.5)	3400–3300, 2800–2500, 1600, 1400, 1200	(D_2O): 1.52–1.8 (dd, 3H, J_{HH} = 7H, J_{HP} = 17 Hz, CH_3CH); 3.5–4.14 (m, 3H, CH_3CH, PCH_2)
4b	i-C_3H_7	54	202–205	$C_5H_{13}ClNO_2P$ (185.5)	3400–3300, 2800–2500, 1600, 1400, 1200	(D_2O): 1.28–1.35 (d, 6H, J = 7 Hz, $(CH_3)_2CH$); 2.4–2.86 (m, 1H, $(CH_3)_2CH$); 4.2–4.72 (m, 3H, PCH_2, $(CH_3)_2CHCH$)
4c	i-C_4H_9	25[b]	184–187	$C_6H_{15}ClNO_2P$ (199.5)	3400–3300, 2800–2500, 1600, 1400, 1200	(D_2O): 1.4–1.5 (d, 6H, J = 5 Hz, $(CH_3)_2CH$); 1.83–2.08 (m, 3H, CH_2CH, $(CH_3)_2CH$); 3.7–4.1 (m, 3H, PCH_2, CH_2CH)
4d	C_6H_5	63	210–212	$C_8H_{11}ClNO_2P$ (226.5)	3400–3300, 2800–2500, 3080, 1600, 1450, 1400, 1200	(D_2O, NaOD): 3.76–3.83 (d, 2H, J_{HP} = 14 Hz, PCH_2); 4.5–4.6 (m, 1H, CHC_6H_5); 7.65 (m, 5H, CHC_6H_5)
4e	$C_6H_5CH_2$	45	217–219	$C_9H_{13}ClNO_2P$ (233.5)	3400–3300, 3080, 2800–2500, 1600, 1450, 1400, 1200	(D_2O, NaOD): 2.93–3.2 (m, 2H, CH_2CH); 3.65 (d, 2H, J_{HP} = 14 Hz, PCH_2); 4.3–4.57 (m, 1H, CH_2CH); 7.7 (s, 5H, $CH_2C_6H_5$)

[a] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.1, N ± 0.2, P ± 0.2.
[b] Low yield of compound **4c** due to poor crystallization.

Table 2. *N*-Tosyl Derivatives **6** of 1-Aminoalkyl(chloromethyl)phosphinic Acids **4**.

Product	Yield (%)	m.p. (°C)	Molecular Formula[a]	IR (KBr) ν (cm^{-1})	^{1}H-NMR (solvent, TMS) δ (ppm)
6a	75	145–147	$C_{10}H_{14}ClNO_4PS$ (310.5)	3100–3000, 1600, 1450, 1400, 1350, 1200	(CD_3OD): 1.66–1.21 (dd, 3H, J_{HH} = 7 Hz, J_{HP} = 17 Hz, CH_3CH); 2.38 (s, 3H, $CH_3C_6H_4$); 3.83–4.47 (m, 3H, CH_3CH, PCH_2); 7.3–7.8 (m, 4H, $CH_3C_6H_4$)
6b	70	179–182	$C_{12}H_{18}ClNO_4PS$ (338.5)	3100–3000, 1600, 1450, 1400, 1350, 1200	(CD_3OD): 0.92–0.97 (d, 6H, J = 5 Hz, $(CH_3)_2CH$); 2.34 (s, 3H, $CH_3C_6H_4$); 3.14 (m, 1H, $(CH_3)_2CH$); 3.96–4.24 (m, 3H, $(CH_3)_2CHCH$, PCH_2); 7.3–7.73 (m, 4H, $CH_3C_6H_4$)
6c	65	176–179	$C_{13}H_{20}ClNO_4PS$ (352.5)	3100–3000, 1600, 1450, 1400, 1350, 1200	(CD_3OD): 0.78–0.84 (d, 6H, J = 5 Hz, $(CH_3)_2CH$); 1.6–2.0 (m, 3H, CH_2CH, $(CH_3)_2CH$); 2.33 (s, 3H, $CH_3C_6H_4$); 3.86–4.08 (m, 3H, $(CH_3)_2CHCH$, PCH_2); 7.32–7.68 (m, 4H, $CH_3C_6H_4$)
6d	69	210–213	$C_{15}H_{16}ClNO_4PS$ (372.5)	3100–3000, 1600, 1450, 1400, 1350, 1200	(DMSO): 3.76–3.83 (d, 2H, J_{HP} = 14 Hz, PCH_2); 4.5–4.6 (m, 1H, CHC_6H_5); 7.1–7.8 (m, 9H, C_6H_5, $CH_3C_6H_4$)[b]
6e	72	114–117	$C_{16}H_{18}ClNO_4PS$ (386.5)	3100–3000, 1600, 1450, 1400, 1350, 1200	(DMSO): 3.4–3.9 (m, 4H, CH_2CH, PCH_2); 4.4–4.65 (m, 1H, CH_2CH); 7.02–7.92 (m, 9H, C_6H_5, $CH_3C_6H_4$)[b]

[a] Satisfactory microanalyses obtained: C ± 0.2, H ± 0.1, N ± 0.2, P ± 0.2.
[b] The peak for the tosyl methyl was obsured by solvent.

Aminomethyl(chloromethyl)phosphinic Acid (3):
The solution of *N*-(hydroxymethyl)benzamide (15.1 g, 0.1 mol) in glacial acetic acid (40 ml) is slowly added during 20 min to stirred dichloro(chloromethyl)phosphine (15.15 g, 0.1 mol). A strong exothermic effect with evolution of hydrogen chloride is observed. The mixture is then heated under reflux for 1.5 h, and acetic acid is removed on a rotary evaporator under reduced pressure with heating on a boiling water bath. The oily residue is then hydrolyzed with conc. hydrochloric acid (60 ml) under reflux for 8 h. The solution is cooled and volatile products are removed on a rotary evaporator under reduced pressure with heating on a boiling-water bath. The dry residue is then dissolved in methanol (70 ml) and treated with propylene oxide until precipitation is complete (5 ml). The precipitate is collected by filtration. Crude product is dissolved in water (40 ml) and precipitated with methanol. The precipitate is collected by filtration and washed with methanol to give **3** as a white powder; yield: 10.72 g (75%); m.p. 208–209 °C.

The purity of acid **3** is assayed by TLC (Silica gel 60 F_{254} plates, developed with butanol/acetic acid/pyridine/water, 6:6:3:5). See Table 1.

1-Aminoalkyl(chloromethyl)phosphinic Acids 4; General Procedure:
Freshly distilled aldehyde (0,12 mol) is slowly added (15–20 min) to a stirred mixture of benzyl carbamate (15.3 g, 0,1 mol), dichloro(chloromethyl)phosphine (15.15 g, 0.1 mol) and glacial acetic acid (20 ml). A strong exothermic effect is observed. The mixture is heated under reduced pressure with heating on a boiling water bath. The oily residue is hydrolyzed with conc. hydrochloric acid (50 ml) under reflux for 30 min. The solution is extracted with toluene (3 × 30 ml) and the water phase is evaporated on a rotary evaporator under reduced pressure with heating on a boiling-water bath. The dry residue is dissolved in methanol (50 ml) and treated with propylene oxide until the precipitation is complete (5 ml). The precipitate is collected by filtration. The crude product **4** is dissolved in water (40 ml) and precipitated by the addition

of methanol. The precipitate is collected by filtration. The purity of compounds **4** is assayed by TLC (Silica gel $60\,F_{254}$ plates, developed with butanol/acetic acid/pyridine/water, 6:6:3:5). Yields and physical data of products **4** are reported in Table 1.

***N*-Tosyl Derivatives 6 of 1-Aminoalkyl(chloromethyl)phosphinic Acids 4:** The compounds 6 (Table 2) were prepared according to Ref. and purified by recrystallization from methanol.

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