A Convenient Synthesis of 5-(1-Aminoalkyl)-1*H*-1,2,4-triazoles

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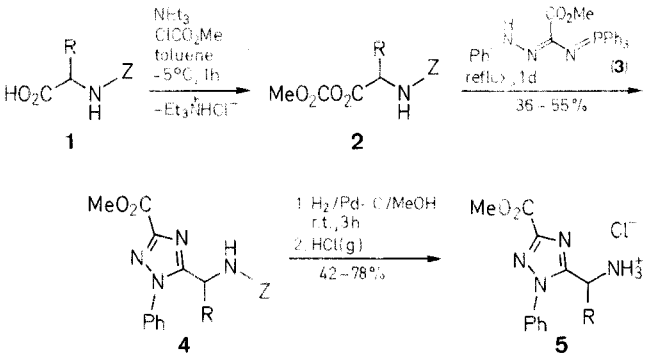
5-(1-Aminoalkyl)-3-methoxycarbonyl-1-phenyl-1H-1,2,4-triazoles **5** were prepared from *N*-benzyloxycarbonyl-protected α-amino acids by reaction of the corresponding mixed anhydrides **2** with methyl phenylhydrazono(triphenylphosphoranylideneamino)acetate (**3**) and subsequent deprotection.

In view of the extensive interest of 1,2,4-triazoles in applicative areas such as agrochemicals and pharmaceuticals,[1] new synthetic entries to this class of compounds may be advisable. As a part of our research program dealing with *N*-(triphenylphosphoranylidene)alkanamide phenylhydrazones as intermediates for the construction of the 1,2,4-triazole ring,[2-4] we have developed a convenient synthesis of 5-(1-aminoalkyl)-1*H*-1,2,4-triazoles.



1, 2, 4, 5	R	1, 2, 4, 5	R
a	H	**d**	*i*-Bu
b	Me	**e**	$PhCH_2$
c	*i*-Pr		

The starting materials for the title compounds were commercially available *N*-protected α-amino acids **1** ($Z = CO_2CH_2Ph$), which were transformed into the mixed anhydrides **2** according to the literature method.[5] Treatment of the intermediates **2** with the iminophosphorane **3**[2] in boiling toluene led to the triazole derivatives **4**, which were obtained in a pure state by chromatography to separate triphenylphosphine oxide usually formed as a by-product (see Table 1). The conversion of **1** to **4** can well be carried out following a one-pot procedure without isolating the mixed anhydride **2**; however, removal of triethylammonium chloride prior to the addition of **3** is necessary in order to avoid carbon dioxide extrusion from **2**, a reaction which is known to suffer catalysis by trialkylammonium halides.[6]

Table 1. 5-[1-(*N*-Benzyloxycarbonylamino)alkyl]-3-methoxycarbonyl-1-phenyl-1*H*-1,2,4-triazoles **4**

Product	Yield (%)	mp (°C)[a]	Molecular Formula[b]	IR (Nujol) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) *m/z*
4a	55	107	$C_{19}H_{18}N_4O_4$ (366.4)	3315, 1740, 1630	3.95 (s, 3H); 4.48 (d, 2H, J = 7); 4.97 (s, 2H); 6.15 (t, 1H, J = 7); 7.21 (s, 5H); 7.40 (s, 5H)	366 (M^+)
4b	41	133	$C_{20}H_{20}N_4O_4$ (380.4)	3300, 1735, 1670	1.51 (d, 3H, J = 7); 4.05 (s, 3H); 4.9–5.2 (m, 1H); 5.06 (s, 2H); 5.60 (d, 1H, J = 9); 7.28 (s, 5H); 7.51 (s, 5H)	380 (M^+)
4c	36	60–61	$C_{22}H_{24}N_4O_4$ (408.5)	3230, 1740, 1695	0.68 (d, 3H, J = 7); 0.9 (d, 3H, J = 7); 1.9–2.3 (m, 1H); 4.06 (s, 3H); 4.6–5.0 (m, 1H); 5.15 (s, 2H); 5.62 (d, 1H, J = 9); 7.34 (s, 5H); 7.61 (s, 5H)	408 (M^+)
4d	38	oil	$C_{23}H_{26}N_4O_4$ (422.5)	3280, 1740, 1705	0.7–0.9 (m, 6H); 1.5–2.0 (m, 3H); 3.97 (s, 3H); 5.05 (s, 2H); 4.9–5.2 (m, 1H); 6.04 (d, 1H, J = 9); 7.25 (s, 5H); 7.4–7.7 (m, 5H)	422 (M^+)
4e	43	53	$C_{26}H_{24}N_4O_4$ (456.5)	3280, 1745, 1710	3.17 (d, 2H, J = 7); 4.00 (s, 3H); 4.9–5.25 (m, 1H); 5.06 (s, 2H); 6.01 (d, 1H, J = 9); 6.7–7.5 (m, 15H)	456 (M^+)

[a] From diisopropyl ether.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, N ±0.30.

Table 2. 5-(1-Aminoalkyl)-3-methoxycarbonyl-1-phenyl-1*H*-1,2,4-triazole Hydrochlorides **5**

Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (Nujol) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS) δ, J (Hz)	$[\alpha]_D^{20}$ (c = 0.6)[b]
5a	68	115 (dec)	$C_{11}H_{13}ClN_4O_2$ (268.7)	3100–2600 (br), 1735	3.95 (s, 3H); 4.62 (s, 2H); 7.63 (s, 5H); 9.3 (br s, 3H)	–
5b	61	84 (dec)	$C_{12}H_{15}ClN_4O_2$ (282.7)	3100–2400 (br), 1715	1.52 (d, 3H, J = 7); 3.97 (s, 3H); 4.54 (m, 1H); 7.63 (s, 5H); 9.05 (br s, 3H)	– 5.7°
5c	78	125 (dec)	$C_{14}H_{19}ClN_4O_2$ (310.8)	3100–2500 (br), 1740	0.78 (d, 3H, J = 7); 1.01 (d, 3H, J = 7); 2.3–2.6 (m, 1H); 3.95 (s, 3H); 4.4–4.7 (m, 1H); 7.4–7.9 (m, 5H); 9.3 (br s, 3H)	– 6.3°
5d	76	105 (dec)	$C_{15}H_{21}ClN_4O_2$ (324.8)	3100–2500 (br), 1735	0.55 (d, 3H, J = 7); 0.73 (d, 3H, J = 7); 1.7–2.2 (m, 3H); 3.98 (s, 3H); 4.7–5.0 (m, 1H); 7.4–7.8 (m, 5H); 9.3 (br s, 3H)	– 11.1°
5e	42	229	$C_{18}H_{19}ClN_4O_2$ (358.8)	3100–2600 (br), 1720	2.9–3.1 (m, 2H); 3.77 (s, 3H); 4.1–4.4 (m, 1H); 6.5–7.2 (m, 10H); 9.3 (br s, 3H)	+ 92.0°

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.30, N ±0.30.

[b] Solvent: EtOH/H_2O, 3 : 2 *v/v*.

To remove the protection of the amino group, compounds **4** were submitted to catalytic hydrogenation in methanol (see Table 2). It is to be noted that, when the starting material was an enantiomerically pure substrate, the final product was found to be optically active.

Melting points were taken using a Büchi apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 298 spectrophotometer. ^{1}H-NMR spectra were taken using a Varian EM-390 instrument. Mass spectra were obtained using a VG model 70 EQ spectrometer. Observed rotations at the Na-D line were obtained at 20°C using a Perkin-Elmer 241 polarimeter.

1*H*-1,2,4-Triazoles 4; General Procedure:
A solution of *N*-benzyloxycarbonyl-L-α-amino acid **1** (9.0 mmol) and NEt_3 (9.0 mmol) in dry toluene (50 mL) is cooled at −5°C, then methyl carbonochloridate (9.0 mmol) is added. After 1 h stirring at −5°C, $Et_3\overset{+}{N}H\ Cl^-$ is eliminated by centrifugation, a solution of phosphine imide **3**[2] (1.5 mmol) in dry toluene (15 mL) is added, and the mixture is refluxed for 1 d. The solvent is removed under reduced pressure, and the residue is chromatographed on a silica gel column (500 g; 70–230 mesh) with Et_2O as eluent to give triazole **4** (Table 1).

Catalytic Hydrogenation of 1*H*-1,2,4-Triazoles 4; General Procedure:
To a solution of triazole **4** (1.0 mmol) in MeOH (20 mL) the catalyst (5% Pd on C, 200 mg) is added. The mixture is hydrogenated at atmospheric pressure for 3 h, the catalyst is eliminated by filtration over celite, and dry gaseous HCl is bubbled into the solution, the solvent is partly removed under reduced pressure, and triazole hydrochloride **5** is isolated by filtration (Table 2).

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