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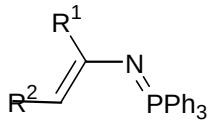
SYNTHESIS OF SUBSTITUTED PYRROLES FROM *N*-VINYLIC PHOSPHAZENES DERIVED FROM ß-AMINO ACIDS AND α-BROMO KETONES#

Francisco Palacios* Esther Herrán, and Gloria Rubiales

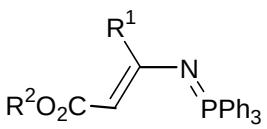
Department of Organic Chemistry, Faculty of Pharmacy, University of the Basque Country,
P.O. Box 450, 01080 Vitoria, Spain
*E-mail: qoppagaf@vf.ehu.es

Abstract- Synthesis of di-, tri- and tetrasubstituted pyrroles by reaction of *N*-vinylic phosphazenes derived from β-amino acids with α-bromo ketones is described.

Pyrroles[1] are very important compounds, not only because they occur in a large number of natural products, but also because they are constituents of neutral pigments, enzymes and biologically active compounds of interest to medicinal chemistry.[2] These properties have stimulated extensive research on the regioselective synthesis[3] of pyrrole derivatives and in the development of a methodology for accessing these heterocycles.[4] Phosphazenes or iminophosphoranes,[5] nitrogen analogues of phosphorus ylides, are interesting substrates for the construction of C=N double bonds in acyclic compounds and heterocycles.[6] Likewise, *N*-vinylic phosphazenes (**Ia**)[7] containing an aryl substituent in the 3-position (R^1= Ph, R^2=H, Figure 1), and indenyl- (**Ib**) (R^1=R^2=C_7H_6) or azulene-phosphazenes (**Ic**) (R^1=R^2=C_8H_{11}) have been demonstrated as excellent starting substrates for the preparation of pyrroles with α-halo ketones.[8]



Ia = (R^1=Ph, R^2=H)
Ib = (R^1=R^2= C_7H_6)
Ic = (R^1=R^2= C_8H_{11})



IIa = (R^1=H, Me, Ph)
IIb = (R^1=CO_2R^2)

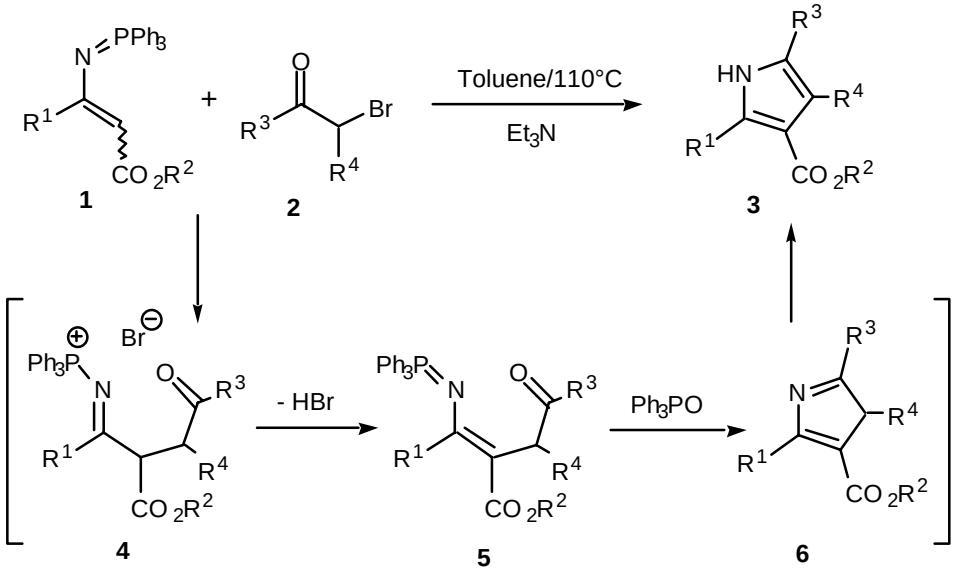
Figure 1

In this context, we have widely used *N*-vinylic phosphazenes derived from β-amino acids (**IIa**) (R^1=H, Me, Ph) and derived from dehydroaspartic esters (**IIb**) (R^1=CO_2R) in the preparation of azadienes[9] and as key intermediates in the preparation of five-,[10] six-membered heterocycles,[9,11] and polycyclic compounds.[12] Continuing with our interest in the synthesis of nitrogen heterocycles and making use of the ambident character of *N*-vinylic phosphazenes (**IIb**) towards electrophiles reaction at nitrogen (1,2-

Dedicated to Professor A. I. Meyers on the occasion of his 70th birthday

addition) of the phosphazene group and reactions at the γ-C-atom (1,4-addition) as protected primary enamines, we here report an easy synthesis of substituted pyrroles containing carboxylate groups from *N*-vinylic phosphazenes derived from β-amino acids and α-bromo ketones.

The reaction of phosphazenes (**1**) (Scheme 1) with α-bromo ketones (**2**) in toluene and triethylamine afforded the di-, tri-, or tetrasubstituted pyrroles (**3**) with moderate yields (Table 1). Compounds (**3**) were characterized on the basis of their NMR spectroscopic data and MS spectrometry (Table 2). Formation of these compounds could be explained by an enamine-type alkylation process (1,4-addition) to give the intermediate (**4**), whose deprotonation (-HBr) generates a new phosphazene (**5**). Subsequent intramolecular Aza-Wittig reaction of **5** (1,2-addition), followed by hydrogen migration from **6** could give **3**, in a similar manner to that observed for simple conjugated phosphazenes.[7,8]



Scheme 1

Table 1. Pyrroles (**3**)

Entry	Compd	R^1	R^2	R^3	R^4	Time (h)	Yield (%)[a]	m p [^oC][b]
1	**3a**	H	Et	Me	H	72	47	oil
2	**3b**	H	Et	Ph	Ph	48	43	193-194
3	**3c**	H	Et	Ph	H	72	42	115-116
4	**3d**	Me	Me	Ph	H	48	57	141-142
5	**3e**	Ph	Et	Ph	H	72	41	151-152
6	**3f**	CO_2Me	Me	Ph	Ph	72	57	173-175

[a] Yield of pure compounds after column chromatography. [b] After recrystallization from CH_2Cl_2/hexane.

Therefore, this process provides an easy and useful route to 1H-pyrroles (**3a-e**) derived from amino acids and 1H-pyrrole (**3f**) derived from dehydroaspartic ester. Compounds with these substructures could be

very useful in organic synthesis and for the preparation of biologically active derivatives of interest to medicinal chemistry.[1,2]

Table 2. Selected spectral data for compounds (**3**)

Compd	^{1}H-NMR ($CDCl_3$)[a] δ (ppm)	^{13}C-NMR ($CDCl_3$)[a] δ (ppm)	IR[b] υ(cm^{-1})	MS[c] (m/z)
3a	1.26 (t, 3H, J = 7.2 Hz, CH_3), 2.18 (s, 3H, CH_3), 4.19 (q, 2H, J = 7.3 Hz, CH_2), 6.23 (s, 1H, =CH), 7.20 (d, 1H, J = 3.1 Hz, =CH), 8.60 (s, 1H, NH)	12.7 (CH_3), 14.4 (CH_3), 59.5 (OCH_2), 106.9 (=CH), 116.5 (C=), 122.4 (=CH), 128.7 (C=), 165.3(COO)	3300 NH) 1678 (COO)	153 [M^+, 45 %]
3b	1.08 (t, 3H, J = 7.2 Hz, CH_3), 4.07 (q, 2H, J = 7.3 Hz, CH_2), 7.06-7.33 (m, 10H, Harom.), 7.47 (d, 1H, J = 3.2 Hz, =CH), 8.59 (s, 1H, NH)	14.1 (CH_3), 59.5 (OCH_2), 116.4 (C=), 122.9 (C=), 124.2 (=CH), 126.3-132.1 (m, 12C) 134.9 (C=), 164.7(COO)	3320 (NH) 1677 (COO)	291 [M^+, 100 %]
3c	1.29 (t, 3H, J = 7.2 Hz, CH_3), 4.24 (q, 2H, J = 7.3 Hz, CH_2), 6.84 (d, 1H, J = 1.5 Hz, =CH), 7.15-7.44 (m, 6H, Harom and =CH), 8.92 (s, 1H, NH)	14.4 (CH_3), 59.5 (OCH_2), 106.5 (=CH), 117.9 (C=), 124.1-128.9 (m, 6C), 133.0 (C=), 165.1(COO)	3294 (NH) 1670 (COO)	215 [M^+,69 %]
3d	2.51 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.76 (d, 1H, J = 2.9 Hz, =CH), 7.11-7.40 (m, 5H, Harom.), 8.61 (s, 1H, NH)	13.3 (CH_3), 50.9 (OCH_3), 107.3 (=CH), 113.0 (C=), 123.7-130.1 (m, 6C), 131.8 (C=), 136.3 (C=), 166.0 (COO)	3300 (NH) 1670 (COO)	215 [M^+,100 %]
3e	1.16 (t, 3H, J = 7.2 Hz, CH_3), 4.17 (q, 2H, J = 7.3 Hz, CH_2), 6.95 (d, 1H, J = 2.9 Hz, =CH), 7.29-7.59 (m, 10H, Harom), 8.59 (s, 1H, NH)	14.3 (CH_3), 59.8 (OCH_2), 109.1 (=CH), 113.8 (C=), 124.0-129.0 (m, 10C), 131.5 (Carom.), 131.7 (Carom.), 131.9 (C=), 137.7 (C=), 164.8 (COO)	3296 (NH) 1678 (COO)	291 [M^+, 100 %]
3f	3.67 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 7.13-7.20 (m, 10H, Harom.), 9.56 (s, 1H, NH)	52.1 (OCH_3), 52.2 (OCH_3), 119.8 (C=), 122.9 (C=), 123.2 (C=), 127.1-129.8 (m, 10C), 130.7 (Carom.), 133.1 (C=), 133.3 (C=), 160.7 (COO), 166.2 (COO)	3291 (NH) 1681 (COO) 1729 (COO)	335 [M^+, 83%]

[a] Obtained on a Varian VXR 300 Spectrometer.[b] Recorded in a Nicolet FTIR Magna 550.[c] Obtained on a Hewlett Packard 5890 Spectrometer.

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