Synthesis of 3,4-Dihydro-2*H*-pyrido[1,2-*b*]isoindol-1-one and 3,4-Dihydro-2*H*-pyrido[1,2-*b*]pyrrolidin-1-one Functionalized at the C-6 Position by an Intramolecular Horner-Wadsworth-Emmons Reaction

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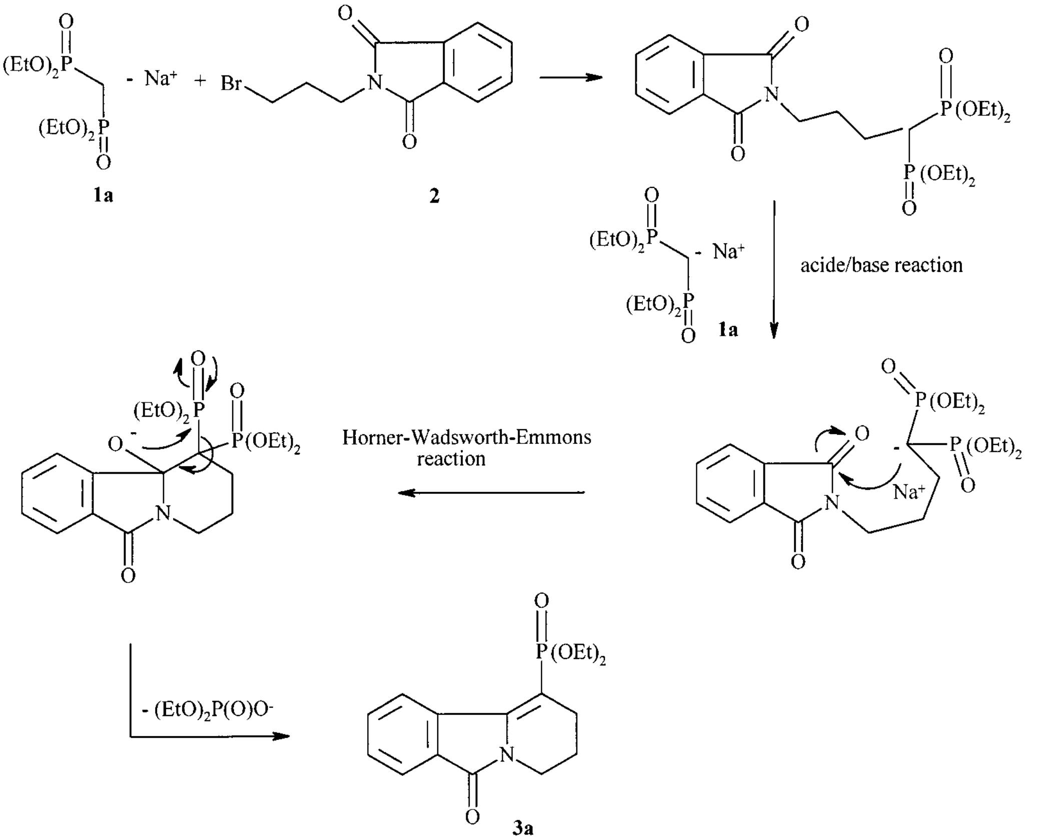
Keywords: Methylene-1,1-bisphosphonate / 3-Bromoalkylimide / Horner-Wadsworth-Emmons reaction / Phosphonate complexes / Heterocyclic compounds / Cyclizations

Novel polyheterocycles were prepared from a new annellation reaction which proceeds by nucleophilic substitution followed by an intramolecular Horner-Wadsworth-Emmons reaction between imides and β-functionalized phosphonates.

While investigating the alkylation of tetraethyl methylene-1,1-bisphosphonate (**1**) by various ω-bromoalkylphthalimides in order to prepare ω-aminoalkylidene-1,1-bisphosphonate derivatives, we noticed that when the reaction started from 3-bromopropylphthalimide (**2**), 6-(diethylphosphono)-3,4-dihydro-2*H*-pyrido[1,2-*b*]isoindol-1-one (**3a**) was formed. From both fundamental and experimental points of view this result seemed to us quite interesting so we began to consider the mechanism involved in the formation of compound **3a** with the hope of extending this reaction to other β-functionalized phosphonates. It seemd to us that the formation of **3a** could be explained by an intramolecular Horner-Wadsworth-Emmons[1] reaction made possible by an acid-base exchange (Scheme 1).



Scheme 1. Proposed mechanism

A preliminary attack of a carbanion at the carbonyl group was excluded because the tetraethyl methylene-1,1-

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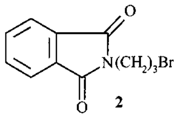
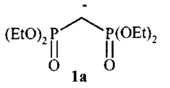
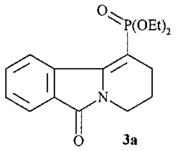
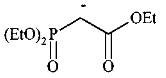
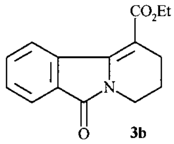
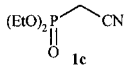
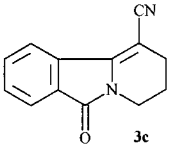
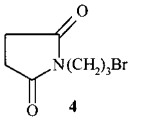
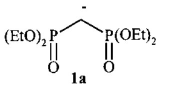
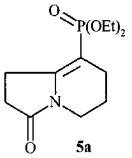
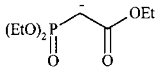
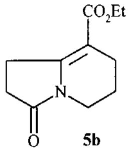
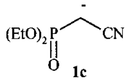
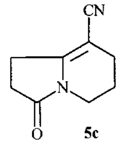
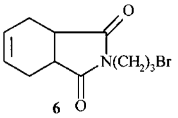
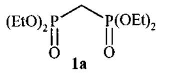
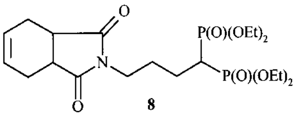
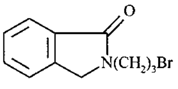
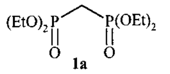
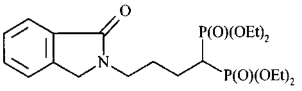
1434−193X/99/1212−3489 $ 17.50+.50/0

Table 1. Heterocycles prepapared

Imide	Carbanion	Heterocycle	Time	Yield
 **2**	 **1a**	 **3a**	12h	85%
	 **1b**	 **3b**	8h	92%
	 **1c**	 **3c**	3h	95%
 **4**	 **1a**	 **5a**	22h	78%
	 **1b**	 **5b**	12h	83%
	 **1c**	 **5c**	8h	90%
 **6**	 **1a**	 **8**	12h	82%
 **7**	 **1a**	 **9**	12h	78%

bisphophonate carbanion **(1a)** does not react with *N*-methylphthalimide. This result confirmed the initial nucleophilic substitution. Then, via an acid-base exchange, the substitution product induced an intramolecular Horner-Wadsworth-Emmons reaction, which was facilitated by the formation of the 6-ring compound.

The interest of this reaction is all the more obvious as it is poorly documented. Flitsch et al.[2] have shown the reactivity of the imide function with phosphoranes and have developed the synthetic potential of this reaction.[3] But, to the best of our knowledge, Foucaud et al. are still the only people who have reported the reactivity of the diethyl cyanomethylphosphonate carbanion with substituted succinimides.[4] We therefore developed this sequential nucleophilic substitution/intramolecular Horner-Wadsworth-Emmons reaction using other similar imides (Table 1). Under such conditions, the *N*-3-bromopropylsuccinimide **4** led to the cyclic compound **5a** thus showing that the presence of an aromatic ring such as phthalimide is not essential for achieving the substitution/Horner-Wadsworth-Emmons sequence. *N*-(3-Bromopropyl)-*cis*-hexahydrophthalimide **(6)** gave only the substitution product **8**. This can be explained by the steric hindrance resulting from the nonplanarity of **6**. On the other hand, the imide function is essential for the development of this reaction pathway. With 2-(3-bromopropyl)-1-isoindolinone (**7**), the nucleophilic substitution took place but no further reaction was observed. This result is not surprising as the low reactivity of amides in the Wittig-Horner reaction is well-known.[5]

We then tried to extend the results obtained with tetraethyl methylene-1,1-bisphosphonate **1** to other β-functionalized phosphonates. We obtained the polyheterocycles **3** and **5** in good yields (see Table 1 and the experimental section). Our experimental results emphasised the difference in reactivity of the various carbanions. Irrespective of the imide molecule used, the carbanion of ethyl 2-cyanomethylphosphonate **(1c)** was the most reactive, considerably reducing the reaction times needed for the synthesis of the heterocycles. Moreover, ethyl 2-oxopropylphosphonate did not react because of the partial delocalization of the negative charge to the carbonyl group.

Of the two imides investigated, 3-bromopropylphthalimide **(2)** was the most reactive providing us with the best yields and the shortest reaction times. Compared to succinimide, the aromaticity of the cycle next to the imide function in compound **2** activates the carbonyl function inducing the Horner-Wadsworth-Emmons reaction.

In conclusion, the present study has shown that the imide function is likely to react with phosphonate carbanions by a Horner-Wadsworth-Emmons reaction. A wide selection of reactants should enable the synthesis of functional

Table 2. Physical characteristics of compounds **3a**–**c**, **5a**–**c**, **8** and **9**

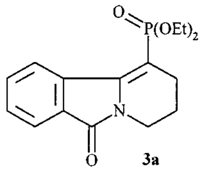
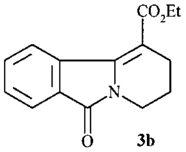
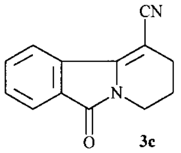
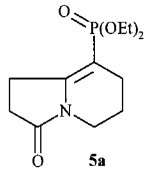
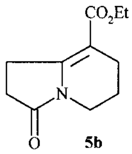
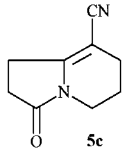
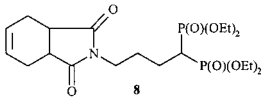
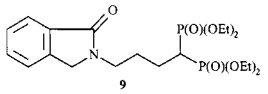
Heterocycle	Molecular Formula	Microanalytical data	Rf (AE/H) mp (°C)
 **3a**	$C_{16}H_{20}NO_4P$ 321.3	Calcd. : C, 59.8; H, 6.3; N, 4.3; P, 9.6 Found : C, 59.5; H, 6.5; N, 4.2; P, 9.4	0.4 (1/2) oil
 **3b**	$C_{15}H_{15}NO_3$ 257.3	Calcd. : C, 70.,0; H, 5.9; N, 5.4 Found : C, 69.1; H, 6.0; N, 5.3	0.26 (1/2) 95
 **3c**	$C_{13}H_{10}N_2O$ 210.2	Calcd. : C, 74.3; H, 4.8; N, 13.3 Found : C, 74.1; H, 7.0; N, 13.2	0.21 (1/1) 92
 **5a**	$C_{12}H_{20}NO_4P$ 273.2	Calcd. : C, 52.7; H, 7.4; N, 5.1; P, 11.3 Found : C, 52.5; H, 7.5; N, 5.0; P, 11.2	0.28 (2/1) oil
 **5b**	$C_{11}H_{15}NO_3$ 209.2	Calcd. : C, 63.1; H, 7.2; N, 6.7 Found : C, 59.9; H, 7.3; N, 6.5	0.27 (1/1) 74
 **5c**	$C_9H_{10}N_2O$ 162.2	Calcd. : C, 66.7; H, 6.2; N, 17.3 Found : C, 66.5; H, 6.4; N, 17.2	0.31 (1/1) 72
 **8**	$C_{20}H_{35}NO_8P_2$ 479.4	Calcd. : C, 50.1; H, 7.4; N, 2..9; P, 12.9 Found : C, 49.8; H, 7.6; N, 2.8; P, 12.7	0.31 (9/1) oil
 **9**	$C_{20}H_{33}NO_7P_2$ 461.4	Calcd. : C, 52.1; H, 7.2; N, 3.0; P, 13.4 Found : C, 48.8; H, 7.4; N, 2.9; P, 13.1	0.32 (AE) oil

Table 3. Spectroscopic data of compounds **3a−c, 5a−c, 8** and **9**

Product	IR (KBr) υ (cm^{-1})	^{1}H NMR (CDCl$_3$) δ, J(Hz)	^{13}C NMR (CDCl$_3$) δ	^{31}P NMR (CDCl$_3$)
3a	1694 1599 1234	1.32 (t, 6H, *J* = 7.1), 1.97 (qn, 2H, *J* = 5.8), 2.64 (q, 2H, *J* = 5.8), 3.79 (t, 2H, *J* = 5.8), 4.1 (qn, 4H, *J* = 7.1), 7.50 (t, 1H, *J* = 7.8), 7.59 (t, 1H, *J* = 7.8), 7.81 (d, 1H, *J* = 7.8), 8.74 (d, 1H, *J* = 7.8)	16.4, 21.0 26.7, 38.5, 62.1, 104.8, 122.8, 126.1, 128.8, 130.0, 132.1, 133.6, 143.4, 166.1	17.9
3b	1706 1688 1598	2.04 (qt, 2H, *J* = 5.9), 2.59 (t, 2H, *J* = 5.9), 3.79 (t, 2H, *J* = 5.9), 7.59 (t, 1H, *J* = 7.5), 7.67 (t, 1H, *J* = 7.5), 7.85 (d, 1H, *J* = 7.5), 8.32 (d, 1H, *J* = 7.5)	14.3, 20.6, 25.5, 38.5, 60.9, 110.8, 122.8, 126.5, 130.1, 130.3, 132.3, 133.8, 140.9, 166.2, 167.1	
3c	2197 1709 1637	1.35 (t, 3H, *J* = 7), 1.97 (qt, 2H, *J* = 5.9), 2.7 (t, 2H, *J* = 5.9), 3.79 (t, 2H, *J* = 5.9), 4.33 (q, 2H, *J* = 7), 7.50 (t, 1H, *J* = 7.4), 7.83 (d, 1H, *J* = 7.4), 8.57 (d, 1H, *J* = 7.4)	20.8, 25.9, 38.4, 77.1, 120.1, 121.8, 125.3, 128.6, 129.1, 132.2, 133.5, 140.8, 166.2	
5a	1714 1635 1250	1.31 (6H, t, *J* = 7), 1.80 (qt, 2H, *J* = 6.1), 2.23 (q, 2H, *J* = 6.1) 2.46-2.51 and 3.05-3.10 (ABXY, 2×2H) 3.53 (2H, t, *J* = 6.1) 4.01 (4H, qn, *J* = 7)	16.1, 22.0, 25.1, 26.9, 29.3, 38.5, 62.4, 98.7, 153.6, 170.4	21.1
5b	1710 1691 1595	1.52 (t, 3H, *J* = 6.8), 1.82 (qt, 2H, *J* = 6) 2.51-2.57 and 2.88-2.94 (ABXY, 2×2H), 3.51 (t, 2H, *J* = 6), 3.89 (q, 2H, *J* = 6.8)	13.8, 20.2, 26.1, 31.0, 32.8, 40.0, 58.6, 101.3, 159.4, 164.3, 171.1	
5c	2192 1698 1635	1.84 (qt, 2H, *J* = 5.9), 2.30 (t, 2H, *J* = 5.9), 2.55-2.60 and 2.90-2.96 (ABXY, 2×2H), 3.53 (t, 2H, *J* = 5.9)	21.0, 23.8, 28.1, 30.8, 38.5, 74.8, 117.4, 161.3, 173.2	
8	1690 1590 1240	1.31 (t, 12H, *J* = 7), 1.92 (qt, 2H, J = 7.2), 2.23 (tq, 2H, *J* = 15.8), 2.54 (tt, 1H, *J* = 24.1), 2.33-2.70 (ABXY, *J* = 12.5), 3.15 (m, 2H), 3.61 (t, 2H, *J* = 7), 4.10 (qn, 8H, *J* = 7), 5.90 (m, 2H)	16.0, 23.2, 26.1, 27.4, 37.2, 39.0, 40.8, 62.2, 126.4, 176.8	23.8
9	1720 1570 1230	1.32 (t, 12H, *J* = 7.1), 1.91 (qt, 2H, *J* = 7.2), 2.21 (tq, 2H, *J* = 15.8), 2.56 (tt, 1H, *J* = 24.1), 2.32-2.71 (ABXY, *J* = 12.5), 3.12 (m, 2H), 3.73 (t, 2H, *J* = 7), 4.10 (qn, 8H, *J* = 7.1), 5.95 (m, 2H)	16.1, 26.5, 28.0, 37.2, 40.2, 51.7, 62.2, 121.7, 126.5, 128.0, 130.3, 143.9, 166.9	23.5

heteropolycycles with possible pharmacological properties, or which can be used to prepare more elaborate heterocycles.[6]

Experimental Section

^{1}H, ^{31}P and ^{13}C NMR spectra were recorded on a BRUKER AC 300 spectrometer, with CDCl$_3$ as solvent and TMS as internal standard. IR spectra were recorded on a FT-IR-BOMEM. Melting points were measured with a Kofler apparatus. Analytical TLC was performed on silica gel plates (Merck, 60F$_{254}$). Chromatography was carried out on silica gel (Merck 60, 70−230 mesh). Triethyl phosphonoacetate (**2a**) and diethyl cyanophosphonate (**2b**) were of commercial origin. Tetraethyl methylene-1,1-bisphosphonate (**2c**) was prepared according to a known procedure.[7]

Preparation of Heterocycles 3, 5 and Bisphosphonates 8, 9: To a suspension of NaH (0.2 g, 8.3 mmol) in THF (20 mL) was added a solution of **1** (4.0 mmol) in THF (5 mL) at 0°C. The mixture was allowed to warm to room temperature and a solution of **2, 4, 6** or **7** (4.0 mmol) in THF (5 mL) was added before heating under reflux for the time given in Table 1. The reaction mixture was hydrolysed with a saturated aqueous solution of NH$_4$Cl (20 mL) and extracted with Et$_2$O (3 × 15 mL). The organic layers were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel. The physical characteristics and spectroscopic data of isolated products are listed in Table 2 and Table 3, respectively.

Acknowledgments

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