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A simple route to novel 2,5-dihydro-1,5,2-diazaphosphinines from primary enamine phosphonates

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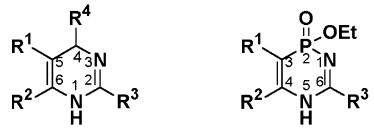
Abstract—A simple method for the preparation of phosphorus-containing pyrimidine analogues such as 4,6-disubstituted-2-ethoxy-2,5-dihydro-1,5,2-diazaphosphinine 2-oxides **5** from primary enamine phosphonates and nitriles is described. A similar strategy is used for the synthesis of the corresponding 4,6-difluorinated-1,5,2-diazaphosphinine 2-oxide derivatives **8**.

Pyrimidines and 1,4-dihydropyrimidines (**I**) are widely used in organic and medicinal chemistry.[1,2] Furthermore, it is known that phosphorus substituents regulate important biological functions,[3] and that the incorporation of phosphorus into organic molecules could increase their biological activity, in a similar way to that reported for other pharmaceuticals.[3] For these reasons, we aimed to incorporate a phosphorus atom into the 1,4-dihydropyrimidine ring systems **I** since phosphorus-containing pyrimidine analogues (**II**, Fig. 1) are expected to play a similar role to that observed in the isosteric analogues **I**, and could possess biological activity. However, very few examples of synthesis of 1,5,2-diazaphosphinine derivatives have been reported[4] and, as far as we know, no examples of 2,5-dihydro-1,5,2-diazaphosphinines (**II**, Fig. 1) have been described.

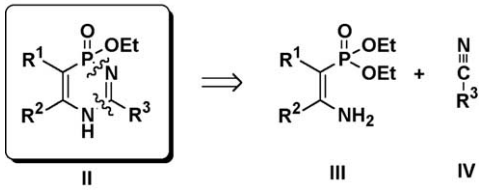
In this context, we have described new methods for the preparation of three,[5] five[6] and six[7] membered phosphorus substituted nitrogen heterocycles from functionalized phosphine oxides and phosphonates and the synthetic uses of amino phosphorus derivatives as starting materials for the preparation of acyclic compounds[8] and phosphorus-containing heterocycles.[4a,9] Continuing with our interest in the synthesis of new phosphorus heterocycles and in the reactivity of functionalized enamines, we report here a simple synthesis of 2,5-dihydro-1,5,2-diazaphosphinines **II** from primary β-enamine phosphonates **III** and nitriles **IV**. Retrosynthetically, we envisaged obtaining these compounds by heterocyclization processes involving, in one step, both the nitrogen–phosphorus (N1–P2) and the carbon nitrogen (N5–C6) bond formations (Fig. 2).

Primary enamines **1**, easily prepared by reaction of phosphonates **2** and nitriles **3** (R^1 = Ph, 2-Fur, 2-Py) in the presence of a base,[10] were used as starting materials for the preparation of heterocycles **5**. Reaction of primary enamines **1** with butyllithium, followed by the addition of nitriles **4** (R^2 = 2-Fur, 2-Py) and subsequent work-up gave 4,6-disubstituted-2-ethoxy-2,5-dihydro-



I II

Figure 1.



II III IV

Figure 2.

Keywords: 1,5,2-diazaphosphinine; enamine; phosphonate; fluorinated compounds.

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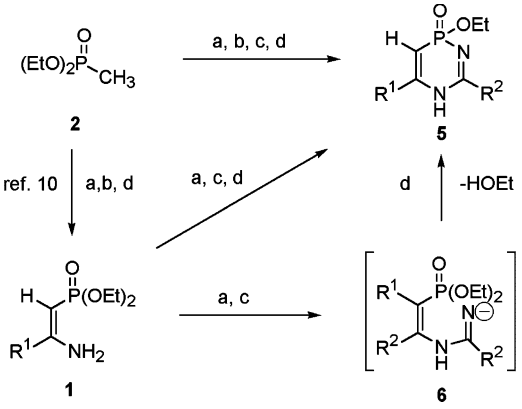
1,5,2-diaza-phosphinine 2-oxides **5**† (Scheme 1) in moderate yields (see Table 1, entries 1–3).[11] Formation of compounds **5** can be explained by nucleophilic addition of metallated enamines to nitriles **4** giving adducts **6**, followed by their subsequent cyclocondensation reaction with the loss of ethanol, in a similar manner to that reported for 1,4,2-benzodiazaphosphepin-5-ones.[12]

From a synthetic point of view, it is noteworthy that these phosphorus analogues of 1,4-dihydropyrimidines **5**, can also be obtained '*one pot*' from phosphonate **2**. Reaction of phosphonate **2** with butyllithium followed by the addition of excess of nitriles **3** (R^1 = 2-Fur, 2-Py) and subsequent work-up gave 2,5-dihydro-1,5,2-diazaphosphinine **5** (Scheme 1) in good yields (see Table 1, entries 4, 5).[13] Therefore, the scope of the reaction was not limited to the preparation of 2,5-dihydro-1,5,2-diazaphosphinine **5** with the same substituents in positions 4 and 6 ($R^1 = R^2$) given that 'phosphadihydropyrimidines' **5** with different substituents (C4 and C6) can also be obtained (see Table 1, entries 1–3).



Scheme 1. Synthesis of 2,5-dihydro-1,5,2-diazaphosphinines. (a) BuLi, THF; (b) R^1CN (**3**); (c) R^2CN (**4**); (d) H_2O.

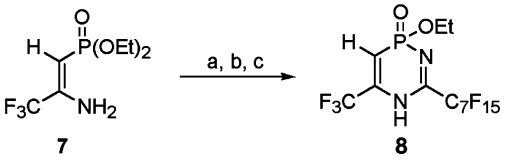
Table 1. Synthesis of 1,5,2-diazaphosphinines **5** and **8**

Entry	Compound	R^1	R^2	Yield[a]
1	**5a**	2-Furyl	2-Pyridyl	46
2	**5b**	Phenyl	2-Furyl	42
3	**5c**	Phenyl	2-Pyridyl	51
4	**5d**	2-Furyl	2-Furyl	62[b]
5	**5e**	2-Pyridyl	2-Pyridyl	74[b]
6	**8**	CF_3	C_7F_{15}	47

[a] Yield refers to pure isolated compounds.
[b] '*One-pot*' procedure from methyl phosphonate diethyl ester **2**.

In the last few years, the development of efficient and mild methods for organofluorine compound synthesis represents a broad area of organic chemistry since the incorporation of a fluorine-containing group into an organic molecule dramatically alters its physical, chemical and biological properties.[14] For these reasons, special interest has been focused on developing synthetic methods for the preparation of fluorinated building blocks as they can be used for the efficient and/or selective preparation of fluorine-containing molecules with biological activity and commercial applications.[15] Therefore, we try to extend the strategy used for the preparation of diazaphosphinines **5** and to explore whether fluorinated primary β-enamino-phosphonate[8a] **7** could also be a useful intermediate for the preparation of fluoro-containing 2,5-dihydro-1,5,2-diaza-phosphinine **8**. Treatment of primary enamine **7** with methyllithium, followed by the addition of perfluorooctanenitrile afforded fluoro-containing 2,5-dihydro-1,5,2-diaza-phosphinine‡ **8** (Scheme 2), in good yield (see Table 1, entry 6).

In conclusion, a simple and efficient strategy for the first synthesis of 2,5-dihydro-1,5,2-diazaphosphinines **5** is described. These phosphorus-containing pyrimidine analogues **5** are obtained from metallated primary enamine phosphonates **1** and nitriles. The reaction can be extended to fluoro substituted 1,5,2-diazaphosphinine **8** when primary fluoroalkyl enaminophosphonate **7** and fluoronitriles are used. 1,4-Dihydropyrimidine derivatives,[1,2] their phosphorus-containing pyrimidine analogues[4] and fluorinated building blocks[14,15] are useful compounds not only for their application in organic synthesis but also for their biological activities. These results may expand the scope and potential of phosphorus and fluorine preparative organic synthesis. Further studies of the use of the enamines as starting materials for the preparation of phosphorus-containing heterocycles are in progress in our laboratory.



Scheme 2. Synthesis of fluorinated 2,5-dihydro-1,5,2-diazaphosphinines. (a) MeLi, THF; (b) $C_7F_{15}CN$; (c) H_2O.

† All new compounds gave satisfactory spectral and elemental analysis. **5d**: White solid; mp 182–183°C; ^{1}H NMR ($CDCl_3$) δ: 1.29 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 4.07 (q, 2H, $^3J_{HH}$ = 7.0 Hz, OCH_2), 5.66 (d, 1H, $^2J_{PH}$ = 2.0 Hz, CH=), 6.49–7.52 (m, 6H, arom.), 8.90 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ: 16.6 (CH_3), 61.7 (OCH_2), 88.6 (d, $^1J_{PC}$ = 153.1 Hz, CH=), 109.8–145.1 (C-arom.), 139.2 (C=N), 146.3 (d, $^3J_{PC}$ = 18.2 Hz, C-*ipso* arom.), 146.7 (C-*ipso* arom.), 147.0 (=C-N) ppm; ^{31}P NMR ($CDCl_3$) δ 7.71 ppm; MS (m/z) 292 (M^+, 49).

‡ Spectral data for **8**: pale yellow solid; mp 113–115°C; ^{1}H NMR ($CDCl_3$) δ: 1.18–1.23 (t, 3H, $^3J_{HH}$ = 7.2 Hz, CH_3), 3.29–3.49 (m, 2H, OCH_2), 5.75 (d, 1H, $^2J_{PH}$ = 4.4 Hz, CH=); ^{13}C NMR ($CDCl_3$) δ: 19.2 (CH_3), 65.5 (OCH_2), 95.6 (d, $^1J_{PC}$ = 149.0 Hz, CH=), 110.5–130.7 (m, CF_3, C_7F_{15}), 157.4–158.7 (q, $^2J_{FC}$ = 28.7 Hz, C-CF_3), 161.2–161.8 (t, $^2J_{FC}$ = 24.2 Hz, C-CF_2); ^{31}P NMR ($CDCl_3$) δ 19.5 ppm; ^{19}F NMR ($CDCl_3$) δ: −73.0, −82.2 (CF_3), −115.7, −115.8, −121.9, −122.7, −123.5, −127.0 (CF_2); MS (m/z) 597 (M^++1, 100).

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11. **General procedure for the preparation of heterocycles 5 from enamines 1**. Butyllithium (1.6 M in hexanes, 1.2 mmol) was added to a stirred solution of enaminophosphonate **1** (1 mmol) in THF at 0°C and under N_2 atmosphere. After 1 h was added the corresponding nitrile **4** (1.2 mmol) solved in THF. The reaction was allowed to warm to rt and stirred until TLC showed the disappearance of enamine **1**. Saturated NH_4Cl solution was added and the organic layer was extracted with CH_2Cl_2, washed twice with water, dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The crude product was purified by column chromatography (AcOEt).
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13. **General procedure for the preparation of heterocycles 5 from phosphonate 2.** Butyllithium (1.6 M in hexanes, 2.4 mmol) was added to a stirred solution of methylphosphonate **2** (1 mmol) in THF at −78°C and under N_2 atmosphere. After 1 h, this solution was added to a solution of the corresponding nitrile **3** (2.4 mmol) in THF. The reaction was allowed to warm to rt and stirred until TLC showed the disappearance of enamine **1**. Saturated NH_4Cl solution was added and the organic layer was extracted with CH_2Cl_2, washed twice with water, dried over anhydrous $MgSO_4$ and the solvent was evaporated under vacuum. The crude product was recrystallized from AcOEt.
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