Unusual C→N migration of phosphoryl group; synthesis of *N′*-phosphorylated amidines

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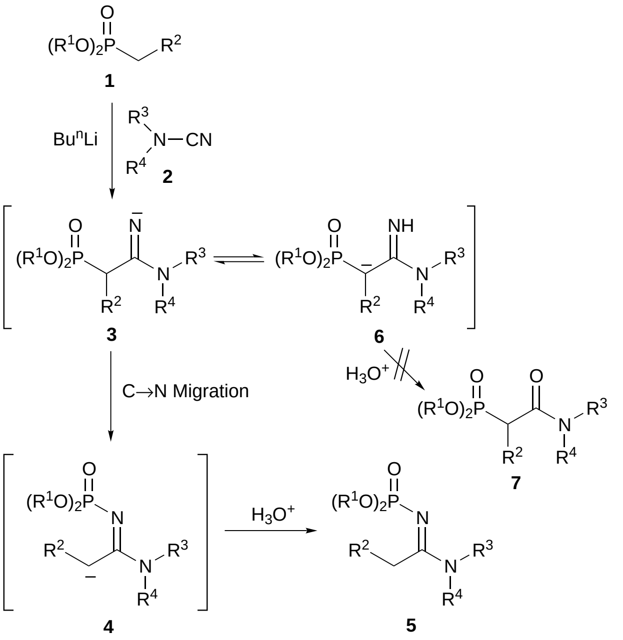
Synthetically and structurally interesting *N′*-phosphoryl amidines were obtained by the reaction of lithiated alkyl phosphonates with *N,N*-dialkylcyanamide *via* an unprecedented migration of the phosphoryl group.

We have been interested in recent years in the reaction of α-lithioalkylphosphonates with nitriles, and we have used these as synthetic intermediates in the preparation of β-keto phosphonates,[1] α,β-unsaturated ketones,[2] deoxybenzoines[3] and *E*-allylic amines.[4] Following on from this work, we turned our attention to the question of whether the reaction of α-lithioalkylphosphonates with cyanamides (instead of nitriles) would generate intermediates **6**, in the hopes of thereby obtaining α,β-unsaturated amides.

To this end, we examined the reaction of α-lithioalkylphosphonates, derived from dialkyl alkylphosphonates, with cyanamides **2** followed by hydrolysis (Scheme 1), and we were surprised to find that the expected compounds **7** were not obtained. Good yields of compounds **5** were obtained instead. Looking closer, we found no evidence for formation of β-carbonyl phosphonate and/or enamine phosphonates on monitoring by TLC. Thus, the most reasonable explanation for the formation of **5** would be the migration of phosphoryl group (**3**→**4**). This unusual C→N migration of a phosphoryl group was observed in all other dialkyl alkylphosphonates and amides tested.‡

As shown in Table 1, the migration works well and gives good yields. All the products were characterized *via* ^{1}H, ^{13}C and ^{31}P NMR spectroscopy and HRMS. The C→N migration is so fast that the reaction was completed within 5 min at −78 °C. The α-lithio anion derived from a benzylphosphonate (**5h** in Table 1) did not give the migration product, and the starting material was recovered. This could be due to the lithiated benzylphosphonate being possibly less nucleophilic than other alkylphosphonates.



Scheme 1

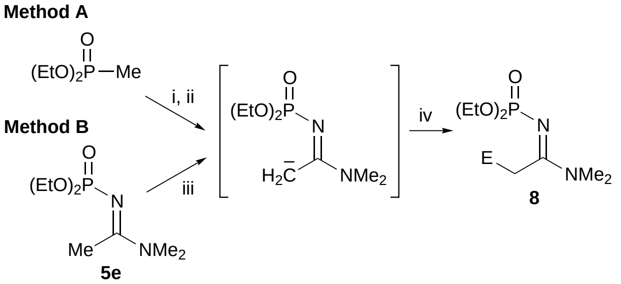
Table 1 Synthesis of *N′*-phosphorylated amidines **5**

Compound	R^1	R^2	R^3	R^4	Yield (%)[a]
5a	Me	H		–(CH$_2$)$_4$–	79
5b	Me	H		–(CH$_2$)$_5$–	82
5c	Et	H		–(CH$_2$)$_4$–	81
5d	Et	H		–(CH$_2$)$_5$–	80
5e	Et	H	Me	Me	87
5f	Et	Allyl	Me	Me	71
5g	Et	Me		–(CH$_2$)$_5$–	73
5h	Et	Ph		–(CH$_2$)$_5$–	No reaction[b]
5i	Pr^i	H		–(CH$_2$)$_5$–	84

[a] Isolated yield. [b] Starting materials were recovered.

Intermediate **3** (or its tautomeric form **6**) seems to be very unstable. In general, amidine derivatives have a zwitterionic character but, in the case of intermediate **3**, the anion interrupts the zwitterionic resonance in the N–C=N linkage, so the migration of the phosphoryl group may not only initiate the zwitterionic resonance, but also stabilize the zwitterionic structure due to p_π–d_π interaction in the P–N bond.[5]§

In order to prepare various *N′*-phosphorylated amidine derivatives **8**, we carried out the reaction shown in Scheme 2 with several electrophiles. Our results are summarized in Table 2. All of the electrophiles gave good yields, even in the one-pot procedure.¶



Scheme 2 *Reagents and conditions*: i, Bu^{n}Li, THF, −78 °C, 1 h; ii, Me$_2$NCN, −78 °C, 10 min; iii, LDA, THF, −78 °C, 1 h; iv, electrophile, −78 °C to room temp., 1 h

Table 2 Synthesis of various *N′*-phosphorylated amidine derivatives **8**

Compound	Electrophile	E in **8**	Method[a]	Yield (%)[b]
8a	D$_2$O	D	A	78
8b	MeI	Me	A	73
8c	Allyl bromide	Allyl	A	68
8d	TMSCl	TMS	A	62
8e	PhCHO	PhCH(OH)	A	41
8e	PhCHO	PhCH(OH)	B	92

[a] See footnote ¶. [b] Isolated yield.

Rearrangements of the phosphoryl groups and other phosphorus containing functional groups are known.[6] Their mechanisms and resulting products are of importance, not only for their synthetic applications and biological activities, but also for understanding the reactivity of the phosphorus atom. However, this is to the best of our knowledge the first example of the C→N migration of a phosphoryl group.

In summary, we have developed an interesting and synthetically useful C→N migration. A study of phosphorylated amidine and its synthetic application is in progress.

Notes and References

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‡ *Typical reaction procedure*: To a stirred solution of $(EtO)_2P(O)Me$ (0.167 g, 1.1 mmol) in dry THF (4 ml) was added Bu^nLi (0.68 ml, 1.1 mmol, 1.6 M in hexanes) at −78 °C under N_2. After stirring for 1 h at −78 °C, Me_2NCN (0.070 g, 1.0 mmol) was added, and the mixture warmed to room temp. After 30 min, saturated aqueous NH_4Cl (5 ml) was added, and stirring continued for 10 min. Extraction with Et_2O (3 × 20 ml), drying and removal of the solvent under reduced pressure gave the crude product. Pure **5e** was obtained (0.1933 g, 87%) by flash column chromatography (EtOAc–MeOH, 10 : 1): δ_H(300 MHz, $CDCl_3$) 1.07–1.12 (t, *J* 17.45, 6 H), 2.16 (s, 3 H), 2.86 (s, 3 H), 2.87 (s, 3 H), 3.83 (dt, J_{P-H} 7.14, J_{H-H} 7.14, 4 H); δ_C(75 MHz, $CDCl_3$) 15.88 (d, J_{P-C} 6.9), 19.40 (d, *J* 4.72), 37.55, 38.23, 61.36 (d, J_{P-C} 6.525), 166.32 (d, J_{P-C} 14.1); δ_P(120 MHz, $CDCl_3$) +6.157; HRMS (EI) calc. 222.1133, found 222.1127.

§ In general, the rotational barrier of the C–N single bond in the amidine moiety is due to its zwitterionic structure. The C–N single bond in *N*′-aryl-*N*,*N*-dimethylacetamidines, which are known for having aryl groups strongly conjugated to the N=C–N moiety, shows a relatively low coalescence temperature (T_c, −60 to 33 °C; ref. 7). However, in the case of *N*′-phosphorylated amidines, the coalescence temperature is about 80 °C (ref. 8), evidence of the extension of the conjugation in the N=C–N linkage to the phosphoryl group, involving strong p_π–d_π conjugation of the P–N bond.

¶ *Method A*: To a stirred solution of $(EtO)_2P(O)Me$ (0.167 g, 1.1 mmol) in dry THF (4 ml) was added Bu^nLi (0.68 ml, 1.1 mmol, 1.6 M in hexanes) at −78 °C under N_2. After stirring for 1 h at −78 °C, Me_2NCN (0.070 g, 1.0 mmol) was added, and the mixture warmed to −5 °C for 30 min. Allyl bromide (0.106 g, 1.0 mmol) was added dropwise and the mixture was warmed to room temp. After 1 h saturated aqueous NH_4Cl (5 ml) was added and stirring continued for 10 min. Extraction with Et_2O (3 × 20 ml), drying and removal of the solvent under reduced pressure gave the crude product. Pure **8c** was obtained (0.178 g, 68%) by flash column chromatography (EtOAc–MeOH, 10 : 1): δ_H(200 MHz, $CDCl_3$) 1.27–1.34 (t, *J* 7.06, 6 H), 2.34–2.46 (m, 2 H), 2.84–2.96 (m, 2 H), 3.00 (s, 3 H), 3.01 (s, 3 H), 4.05 (dq, J_{P-H} 5.02, J_{H-H} 5.02, 4 H), 4.98–5.14 (m, 1 H), 5.77–5.97 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 16.19 (J_{P-C} 6.77), 30.71, 31.91 (J_{P-C} 6), 38.01, 38.31, 115.42, 136.42, 169.01 (J_{P-C} 15.05); HRMS (EI) calc. 262.1446, found 262.1436.

Method B: To a stirred solution of **5e** (0.244 g, 1.1 mmol) in dry THF (4 ml) was added LDA (0.53 ml, 1.1 mmol, 2.0 M in THF) at −78 °C under N_2. After stirring for 1 h at −78 °C, benzaldehyde (1.06 g, 1.0 mmol) was added dropwise. After 1 h, saturated aqueous NH_4Cl (5 ml) was added, and stirring continued for 10 min. Extraction with Et_2O (3 × 20 ml), drying and removal of the solvent under reduced pressure gave the crude product. Pure **8e** was obtained (0.302 g, 92%) by flash column chromatography (EtOAc–MeOH, 10 : 1): δ_H(300 MHz, $CDCl_3$) 1.14–1.18 (t, J_{H-H} 7.09 Hz), 1.18–1.23 (t, J_{H-H} 7.05), 2.88–2.94 (m, 1 H), 2.94 (s, 3 H), 2.96 (s, 3 H), 3.13–3.21 (m, 1 H), 3.87–3.99 (m, 4 H), 4.86 (br d, 1 H), 6.09 (br s, 1 H), 7.09–7.22 (m, 3 H), 7.30–7.33 (m, 2 H); δ_C(75 MHz, $CDCl_3$) 15.99 (d, J_{P-C} 6.975), 38.20, 38.40, 42.63 (d, J_{P-C} 6.375), 61.919 (t, *J* 5.625), 71.04, 125.10, 127.09, 128.15, 144.54, 166.59 (d, J_{P-C} 15.6); δ_P(120 MHz, $CDCl_3$) +8.083; HRMS (EI) calc. 328.1552, found 328.1579.

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