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Efficient and Highly Regioselective Formation of the C═N Double Bond *via* Phosphoryl Thiourea Compounds†

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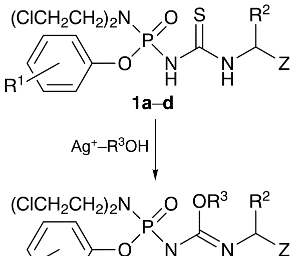
Desulfurization of open chain phosphoryl thiourea compounds utilizing the Ag^+–ROH system under mild conditions affords, regioselectively, depending upon the substrates used, the corresponding imino-ester derivatives in good yields.

N-Substituted imino-esters are intermediates of great synthetic potential owing to the versatile reactivities of the carbon–nitrogen double bond.[1–4] It is reported in the literature that oxidation of the sulfur of a thiourea appears to be a facile and efficient approach to producing the C═N double bond.[5] However, little is known of the regioselective formation of a C═N double bond *via* phosphoryl thiourea compounds.

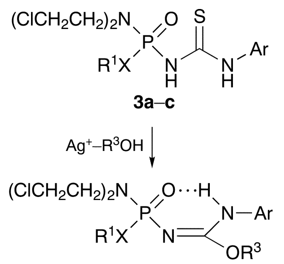
The syntheses of substrates **1** and **3** as well as their good antitumour and antiviral activities have been disclosed in previous papers.[6,7] Thus phosphoryl thiourea derivatives **1a**–**d** with α-amino acid or α-aminoalkylphosphonate moieties were allowed to react with the Ag^+–ROH system to yield regioselectively only products **2a**–**d**, while the substrates **3a**–**c** with N(3)-aryl moieties were treated with the reagent to give regioselectively only compounds **4a**–**c** instead of their corresponding regioselective products **5** and **6**, as depicted in Schemes 1 and 2, respectively.

The desulfurization reaction proceeded smoothly with excess alcohol as the solvent at room temperature to provide the regioselective imino-ester derivatives in excellent yields (83.3–91.6%). The structures of all new compounds, **2a**–**d** and **4a**–**c**, were confirmed by ^1H NMR, ^{31}P NMR, IR, MS spectroscopy and elemental analysis and the regioselectivity of the C═N double bond of the products was determined on the basis of their spectral data, especially ^1H NMR and EI-MS.



2a Z = P(O)(OPh)$_2$, R^1 = *p*-Cl, R^2 = Me, R^3 = Me
b Z = P(O)(OPh)$_2$, R^1 = *o*-Cl, R^2 = *n*-Pr, R^3 = Et
c Z = CO$_2$Et, R^1 = *p*-Cl, R^2 = *s*-Bu(*dl*-isoLeu), R^3 = Me
d Z = CO$_2$Et, R^1 = *p*-Cl, R^2 = CH$_2$Ph(*l*-Phe), R^3 = Et

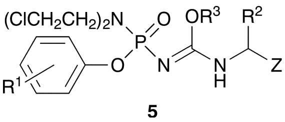
Scheme 1



4a R^{1}X = *p*-ClC$_6$H$_4$O, R^3 = Et, Ar = *o*-ClC$_6$H$_4$
b R^{1}X = *p*-ClC$_6$H$_4$O, R^3 = Pr^i, Ar = C$_5$H$_4$N
c R^{1}X = Pr^{i}NH, R^3 = Et, Ar = *p*-BrC$_6$H$_4$

Scheme 2

The results are summarized in Table 1, which indicates the N—H proton in compounds **2a**–**d** appears as a doublet with a larger coupling constant (J = 8.3–10.4 Hz) which accords with the phosphorus coupling, while in compounds **4a**–**c** it exhibits a singlet at a lower field owing to the fact that there is no phosphorus coupling but six-membered intramolecular hydrogen-bonding exists. In contrast, we can imagine that in the ^1H NMR spectra of the possible products **5** and **6**, however, the N—H protons should appear as two doublets coupled by both the C_α–H ($^3J_{HCNH}$) and the phosphorus atom ($^3J_{PCNH}$) and a doublet owing to the phosphorus coupling ($^2J_{PNH}$), respectively.



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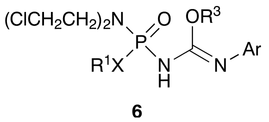

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Table 1 Experimental data of compounds **2a–d** and **4a–c**

Compound	Yield[a] (%)	δ_H (N–H)/ppm (J/Hz)	δ_P/ppm	ν_{max}(C═N)/cm^{-1} (film)
2a	91.6	7.66 (d, J 10.4)	17.08 (s), 11.24 (s)	1638
2b	89.8	7.68 (d, J 9.4)	16.69 (s), 10.76 (s)	1634
2c	88.5	7.60 (d, J 8.3)	11.43, 11.77 (5.2:1)	1636
2d	90.2	7.49 (d, J 8.4)	11.13 (s)	1638
4a	91.2	9.38 (s)	10.23 (s)	1633
4b	83.3	9.97 (s)	—[b]	1629
4c	85.4	9.71 (s)	—	1646

[a]Isolated yield. [b]Data unrecorded.

It is noteworthy that the EI-MS analysis can offer sufficient evidence for the confirmation of the regioselectivity. For instance, compounds **2c** and **2a** are cleaved to give

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cyclic fragments **7** and **8** as base peaks, respectively, which are obtained *via* a six-membered and a four-membered hydrogen-rearrangement, rationalized as in Scheme 3. For compound **4a**, however, the base peak is *m*/*z* 29 (Et^+) *via* a different cleavage mechanism.

Obviously, the high regioselectivity depends upon the structures of the N(3)-substituents of the phosphoryl thiourea substrates. To our knowledge, there exist two possible convincing explanations: (i) the two nitrogen atoms of the carbodiimide intermediate in the mechanism of desulfurization[6,8] are selectively attacked by an hydrogen ion owing to their different electrostatic charges, and (ii) the compounds with lower molecular energy are selectively generated in the reaction. The related quantum chemistry calculation are currently being conducted using the program Sybyl (Version 6.22) of Tripos.

Experimental

IR spectra were obtained as films on a Shimadzu 435 spectrophotometer. The ^1H and ^{31}P NMR spectra were recorded on a JEOL-FX-90Q spectrometer and a Bruker AC-P200 instrument (δ values are in ppm from tetramethylsilane and external 85% phosphoric acid for ^1H and ^{31}P NMR, respectively, in $CDCl_3$; *J* values are given in Hz). Mass spectra were measured on a Hewlett-Packard 5988 spectrometer. Elemental analyses were carried out on a Yana MT-3 analyser.

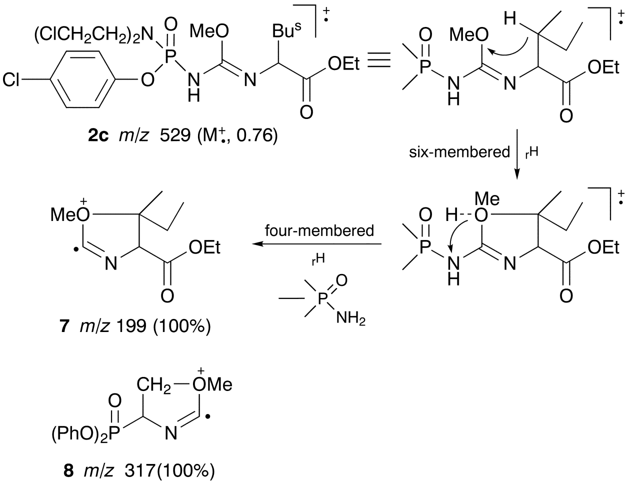
General Procedure for the Preparation of Imino-ester Derivatives **2a**–**d** *and* **4a**–**c**.—The appropriate phosphoryl thiourea (**1a**–**d** and **3a**–**c**, 0.6 mmol) was allowed to react with 1.2 mmol of silver nitrate in 20 ml of anhydrous alcohol at ambient temperature for 10 h, the resultant mixture was then filtered and, after removal of the solvent from the filter liquor under reduced pressure, a small amount of water was added to the residue. The organic product was extracted with $CHCl_3$ (3 × 25 ml) and the layers separated. Combined organic extracts were dried over $MgSO_4$. The solvent was removed under reduced pressure to afford the crude products **2a**–**d** and **4a**–**c**, which were purified by column chromatography on silica gel with a mixture of diethyl ether–light petroleum (bp 60–90 °C) as the eluent. Spectral data and elemental analyses are as follows:

2a: Yield 91.6%; colourless syrup; δ_H ($CDCl_3$) 1.45–1.58 (dd, 3 H, CH_3, *J* 7.2 and 17.9), 3.32–3.59 (m, 8 H, $2ClCH_2CH_2$), 3.52 (s, 3 H, CH_3), 4.35 (m, 1 H, CH), 6.82–7.28 (m, 14 H, $2C_6H_5$ and C_6H_4), 7.66 (d, 1 H, NH, *J* 10.4); δ_P 17.08(s), 11.24(s); ν_{max}/cm^{-1} 3274, 3053, 2950, 1638, 1589, 1484, 1455, 1207, 1183, 1158, 1105, 1021, 989, 933, 833, 761, 707; *m*/*z* 611 (M^+–HCl, 2), 507 (15), 414 (11), 318 (20), 317 (100), 218 (14), 217 (26), 145 (10), 94 (31%) (Found: C, 48.23; H, 4.57; N, 6.62. $C_{26}H_{30}Cl_3N_3O_6P_2$ requires C, 48.11; H, 4.63; N, 6.48%).

2b: Yield 89.8%; colourless syrup; δ_H ($CDCl_3$) 0.94 (t, 3 H, C–C–CH_3), 1.04 (t, 3 H, O–C–CH_3), 1.38–1.88 (m, 4 H, $2CH_2$), 3.42–3.79 (m, 8 H, $2ClCH_2CH_2$), 4.05 (m, 2 H, OCH_2), 4.31 (m, 1 H, CH), 6.86–7.54 (m, 14 H, $2C_6H_5$ and C_6H_4), 7.68 (d, 1 H, NH, *J* 9.4); δ_P 16.69(s), 10.76(s); ν_{max}/cm^{-1} 3267, 3140, 3051, 2952, 1634, 1585, 1477, 1443, 1211, 1182, 1158, 1085, 1057, 1021, 980, 931, 760, 717, 687 (Found: C, 50.25; H, 5.12; N, 6.23. $C_{29}H_{36}Cl_3N_3O_6P_2$ requires C, 50.40; H, 5.21; N, 6.08%).

2c: Yield 88.5%; colourless syrup; δ_H ($CDCl_3$) 0.91–0.96 (m, 6 H, $2CH_3$), 1.23 (t, 3 H, O–C–CH_3), 1.16–1.55 (m, 2 H, CH_2), 1.88 (m, 1 H, CH), 3.41–3.72 (m, 8 H, $2ClCH_2CH_2$), 3.66 (s, 3 H, OCH_3), 4.09–4.32 [m, 3 H, OCH_2 and NCHC(O)], 7.14–7.27 (q, 4 H, C_6H_4), 7.60 (d, 1 H, NH, *J* 8.3); δ_P 11.43, 11.77 (5.2:1); ν_{max}/cm^{-1} 3281, 3058, 2924, 1736, 1636, 1589, 1484, 1462, 1205, 1149, 1124, 1084. 1008, 902, 834; *m*/*z* 529 (M^+, 0.8), 480 (12.6), 458 (7.7), 326 (3.7), 199 (100), 171 (5.6), 142 (6.7), 127 (4.8), 111 (6.1), 92 (6.5), 69 (11.7%) (Found: C, 44.93; H, 5.79; N, 7.82. $C_{20}H_{31}Cl_3N_3O_5P$ requires C, 45.24; H, 5.84; N, 7.92%).

2d: Yield 90.2%; colourless syrup; δ_H ($CDCl_3$) 1.06 (t, 3 H, O–C–CH_3), 1.21 (t, 3 H, C(O)O–C–CH_3), 2.98 (dq, 2 H, CH_2Ph), 3.34–3.62 [m, 8 H, $2ClCH_2CH_2$], 3.96 (m, 2 H, OCH_2), 4.15 [q, 2 H, C(O)OCH_2], 4.38 [m, 1 H, NCHC(O)], 6.92–7.26 (m, 9 H, C_6H_5 and C_6H_4), 7.49 (d, 1 H, NH, *J* 8.4); δ_P 11.13(s); ν_{max}/cm^{-1} 3283, 3078, 2926, 1740, 1638, 1589, 1484, 1460, 1438, 1208, 1159, 1086, 1023, 980, 904, 834, 763, 698 (Found: C, 49.97; H, 5.36; N, 7.43. $C_{24}H_{31}Cl_3N_3O_5P$ requires C, 49.79; H, 5.41; N, 7.26%).



Scheme 3

4a: Yield 91.2%; yellowish syrup; δ_H ($CDCl_3$) 1.26 (t, 3 H, O–C–CH_3), 3.50–3.68 (m, 8 H, $2ClCH_2CH_2$), 4.27 (q, 2 H, OCH_2), 7.02–7.46 (m, 8 H, $2C_6H_4$), 9.38 (s, 1 H, NH); δ_P 10.23(s); ν_{max}/cm^{-1} 3250, 3057, 2910, 1633, 1588, 1484, 1449, 1206, 1125, 1086, 1018, 979, 903, 832, 748; *m*/*z* 511 (M^+, 5.3), 464 (27.6), 386 (32.2), 343 (21.0), 243 (26.1), 204 (58.7), 153 (50.6), 142 (58.1), 127 (68.8), 106 (40.3), 63 (79.2), 29 (100%) (Found: C, 44.64; H, 4.57; N, 8.14. $C_{19}H_{22}Cl_4N_3O_3P$ requires C, 44.44; H, 4.29; N, 8.19%).

4b: Yield 83.3%: colourless syrup; δ_H ($CDCl_3$) 1.18–1.39 (m, 6 H, $2CH_3$), 3.45–3.66 (m, 8 H, $2ClCH_2CH_2$), 4.80 (m, 1 H, OCH), 6.98–8.30 (m, 8 H, C_6H_4 and NC_5H_4), 9.97 (s, 1 H, NH); ν_{max}/cm^{-1} 3387, 3254, 3093, 2971, 1629, 1580, 1487, 1450, 1410, 1217, 1174, 1120, 1100, 1085, 983, 923, 839, 776 (Found: C, 46.37; H, 4.72; N, 11.63. $C_{19}H_{24}Cl_3N_4O_3P$ requires C, 46.20; H, 4.86; N, 11.35%).

4c: Yield 85.4%; colourless syrup; δ_H ($CDCl_3$) 1.12–1.18 (m, 6 H, $2CH_3$), 1.32 (t, 3 H, O–O–CH_3), 2.29 (br, 1 H, NH), 3.17–3.54 (m, 8 H, $2ClCH_2CH_2$), 3.61 (m, 1 H, CH), 4.27 (q, 2 H, OCH_2), 7.04–7.37 (q, 4 H, C_6H_4), 9.71 (s, 1 H, NH); ν_{max}/cm^{-1} 3372, 3226, 3085, 2950, 1646, 1589, 1483, 1453, 1410, 1197, 1147, 1114, 1083, 1025, 974, 930, 817 (Found: C, 39.52; H, 5.17; N, 11.65. $C_{16}H_{26}BrCl_2N_4O_2P$ requires C, 39.34; H, 5.33; N, 11.48%).

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