Solvent-Free Synthesis of Diphenyl [2-(Aminocarbonyl)-1,2-dihydroisoquinolin-1-yl]phosphonates from Isoquinoline, Isocyanates, and Diphenyl Phosphonate

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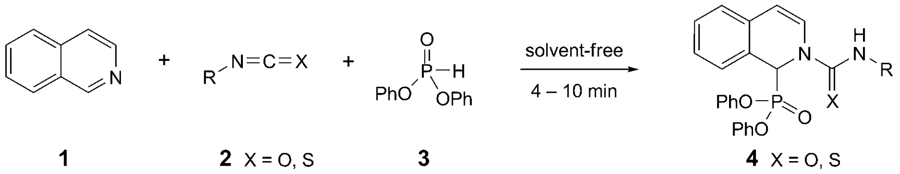
The 1:1 intermediates generated by addition of isoquinoline to isocyanates were trapped by diphenyl phosphonate to yield diphenyl [2-(aminocarbonyl)-1,2-dihydroisoquinolin-1-yl]phosphonates in good yields under solvent-free conditions.

Introduction. – Phosphonate-containing molecules are an important class of active compounds, and their use and synthesis have received attention during the last two decades [1–4]. Among these, α-aminophosphonates are key compounds as analogues of α-amino acids in medicinal chemistry and pharmaceutical industries [5].

As part of our current studies on the synthesis of alkylphosphonates [6–8], we report the results of our studies involving the reactions of zwitterions derived from isoquinoline, isocyanates, and diphenyl phosphonate, which constitute a synthesis of diphenyl α-aminophosphonates **4**.

Results and Discussion. – The reaction of isoquinoline (**1**), isocyanate (or isothiocyanate) **2**, and diphenyl phosphonate (**3**) proceeded smoothly and was complete within 4–10 min. The ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the formation of diphenyl [2-(aminocarbonyl)- or [2-(aminothioxomethyl)-1,2-dihydroisoquinolin-1-yl]phosphonates **4** in 96–99% yield (*Scheme 1* and *Table*).

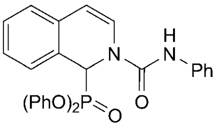
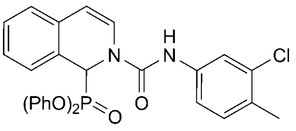
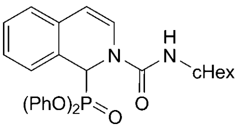
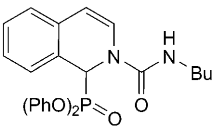
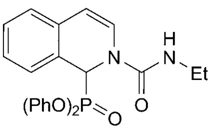
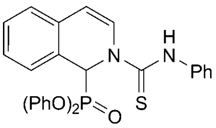
Scheme 1



1 **2** X = O, S **3** **4** X = O, S

The structures of compounds **4a**–**4f** were deduced from their IR and ^{1}H- and ^{13}C-NMR spectra. For example, the ^{1}H-NMR spectrum of **4a** exhibited olefinic (δ(H) 5.47 and 6.80), CH (δ(H) 6.30), and NH (δ(H) 7.92) H-atoms, along with *m*s for the aromatic H-atoms. The ^{1}H-decoupled ^{13}C-NMR spectrum of **4a** showed 22 distinct

Table. *Reaction of Isoquinoline* (**1**) *with Isocyanates* **2a**–**2e**, **2g**, *and* **2h** *or with Isothiocyanate* **2f** *in the Presence of Diphenyl Phosphonate* (**3**) *under Solvent-Free Conditions*

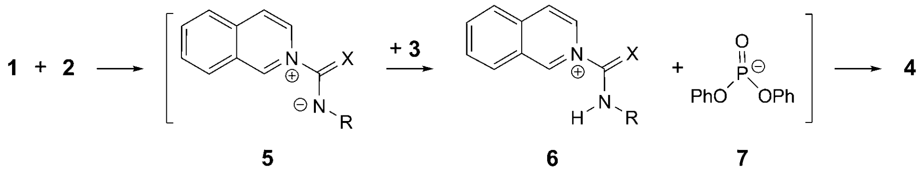
Entry	R–N=C=X	Product		Time [min]	Yield [%]
1	Ph–N=C=O (**2a**)		**4a**	10	98
2	3-Cl–4-Me–C_6H_3–N=C=O (**2b**)		**4b**	4	99
3	cHex–N=C=O (**2c**)		**4c**	7	97
4	Bu–N=C=O (**2d**)		**4d**	8	97
5	Et–N=C=O (**2e**)		**4e**	10	97
6	Ph–N=C=S (**2f**)		**4f**	6	96
7	4-NO_2–C_6H_4–N=C=O (**2g**)	no reaction	–	–	
8	4-Cl–C_6H_4–N=C=O (**2h**)	no reaction	–	–	

resonances that confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic NH, amide C=O, and P=O bands. The ^1H- and ^{13}C-NMR spectra of **4b**–**4f** were similar to those of **4a**, except for the amide moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the zwitterionic intermediate **5** [9][10], formed from **1** and **2**, is protonated by **3** to furnish intermediate **6**, which is attacked by **7** to produce **4** (*Scheme 2*).

In summary, we report a 'green' synthesis of diphenyl [2-(aminocarbonyl)- or [2-(aminothioxomethyl)-1,2-dihydroisoquinolin-1-yl]phosphonates in good yields under

Scheme 2



solvent-free conditions. The present procedure has the advantage that the reaction takes place under noncatalytic conditions, and that the reactants can be mixed without any prior activation or modification.

Experimental Part

General. Compounds **1**–**3** were obtained from *Merck* and used without further purification. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H-, ^{13}C-, and ^{31}P-NMR Spectra: *Bruker-DRX-500-Avance* instrument; in $CDCl_3$ at 500.1, 125.7, and 202 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Finnigan-MAT-8430* mass spectrometer at 70 eV; in m/z (rel. %). Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

Compounds **4**: *General Procedure.* To a stirred mixture of **3** (0.47 g, 2 mmol) and heterocumulene **2** (2 mmol) was added isoquinoline (**1**; 0.26 g, 2 mmol) at r.t. After a short time (4–10 min), solidification occurred, and the solid was washed with cold MeCN (10 ml) to afford the pure desired products.

Diphenyl 1,2-Dihydro-{2-[(phenylamino)carbonyl]isoquinolin-1-yl}phosphonate (**4a**): Yield 0.47 g (98%). White powder. M.p. 148–150°. IR (KBr): 3295 (NH), 3035, 1658 (C=O), 1618, 1585, 1475, 1235 (P=O), 1205, 927, 740. ^{1}H-NMR: 5.47 (*d*, ^3J(H,H) = 7.3, CH); 6.30 (*d*, ^2J(P,H) = 13.4, CH); 6.80 (*d*, ^3J(H,H) = 7.3, CH); 6.92 (*d*, ^3J(H,H) = 7.7, 2 CH); 7.00 (*d*, ^3J(H,H) = 7.7, 2 CH); 7.03–7.12 (*m*, 4 CH); 7.18–7.26 (*m*, 9 CH); 7.34 (*d*, ^3J(H,H) = 7.5, 2 CH); 7.92 (br. *s*, NH). ^{13}C-NMR: 55.2 (*d*, ^1J(P,C) = 156.6, CH–P); 110.5 (CH); 120.0 (*d*, ^3J(C,P) = 2.6, 2 CH); 120.1 (*d*, ^3J(C,P) = 2.6, 2 CH); 123.5 (2 CH); 124.0 (C); 124.8 (CH); 125.0 (*d*, ^3J(C,P) = 2.9, CH); 125.1 (2 CH); 125.2 (C); 127.2 (CH); 127.3 (CH); 127.4 (C); 128.7 (CH); 128.9 (CH); 129.0 (CH); 129.4 (2 CH); 129.6 (2 CH); 131.4 (*d*, ^3J(C,P) = 3.3, CH); 150.1 (*d*, ^2J(C,P) = 10.5, C); 150.2 (*d*, ^2J(C,P) = 10.5, C); 152.3 (C=O). ^{31}P-NMR: 11.1. EI-MS: 482 (2, M^+), 234 (20), 170 (10), 130 (50), 129 (100), 119 (52), 94 (95), 92 (40), 77 (42), 65 (48), 51 (51), 39 (80). Anal. calc. for $C_{28}H_{23}N_2O_4P$ (482.47): C 69.71, H 4.80, N 5.81; found: C 69.80, H 4.75, N 5.72.

Diphenyl {2-{[(3-Chloro-4-methylphenyl)amino]carbonyl}-1,2-dihydroisoquinolin-1-yl}phosphonate (**4b**): Yield 0.52 g (99%). White powder. M.p. 157–159°. IR (KBr): 3285 (NH), 3000, 1654 (C=O), 1620, 1578, 1506, 1480, 1208 (P=O), 932, 756. ^{1}H-NMR: 2.31 (*s*, Me); 5.94 (*d*, ^3J(H,H) = 7.5, CH); 6.27 (*d*, ^2J(P,H) = 12.9, CH); 6.79 (*d*, ^3J(H,H) = 7.6, CH); 6.92 (*d*, ^3J(H,H) = 8.4, 2 CH); 7.02 (*d*, ^3J(H,H) = 8.0, 2 CH); 7.09–7.15 (*m*, 4 CH); 7.20–7.31 (*m*, 8 CH); 7.42 (*s*, 1 CH); 7.96 (br. *s*, NH). ^{13}C-NMR: 28.4 (Me); 47.5 (*d*, ^1J(P,C) = 160.5, CH–P); 110.8 (CH); 118.5 (CH); 120.2 (*d*, ^3J(C,P) = 4.0, 2 CH); 120.8 (*d*, ^3J(C,P) = 2.0, 2 CH); 124.9 (CH); 125.0 (CH); 125.1 (CH); 125.2 (CH); 125.3 (CH); 127.5 (C); 128.0 (*d*, ^2J(C,P) = 2, C); 129.2 (CH); 129.6 (2 CH); 129.8 (CH); 130.9 (2 CH); 131.2 (CH); 131.5 (C); 134.4 (C); 135.2 (C); 137.2 (CH); 150.1 (*d*, ^2J(C,P) = 11, C); 150.2 (C); 152.4 (C=O). ^{31}P-NMR: 11.6. EI-MS: 530 (1, M^+), 234 (22), 170 (12), 167 (52), 140 (38), 130 (51), 129 (100), 113 (47), 94 (92), 77 (44), 51 (50), 39 (75). Anal. calc. for $C_{29}H_{24}ClN_2O_4P$ (530.95): C 65.60, H 4.56, N 5.28; found: C 65.52, H 4.61, N, 5.35.

Diphenyl {2-[(Cyclohexylamino)carbonyl]-1,2-dihydroisoquinolin-1-yl}phosphonate (**4c**): Yield 0.47 g (97%). White powder. M.p. 143–145°. IR (KBr): 3330 (NH), 2910, 1661 (C=O), 1619, 1583, 1478, 1248 (P=O), 1211, 945, 764. ^{1}H-NMR: 1.20 (*m*, 3 CH); 1.39 (*m*, 2 CH); 1.61–1.70 (*m*, 3 CH); 1.95 (*m*, 2 CH); 3.72 (*m*, CH–N); 5.35 (br. *s*, NH); 5.92 (*d*, ^3J(H,H) = 5.7, CH); 6.30 (*d*, ^2J(P,H) = 15.0, CH); 6.71 (*d*, ^3J(H,H) = 7.4, CH); 6.98–7.01 (*m*, 4 CH); 7.09 (*d*, ^3J(H,H) = 7.5, CH); 7.11–7.16 (*m*, 2 CH);

7.24–7.29 (*m*, 5 CH); 7.32–7.34 (*m*, 2 CH). ^{13}C-NMR: 24.8 (CH$_2$); 24.9 (CH$_2$); 25.6 (CH$_2$); 33.3 (CH$_2$); 33.5 (CH$_2$); 50.0 (CH–N); 54.9 (*d*, ^{1}J(P,C) = 155.0, C–P); 110.0 (CH); 120.2 (*d*, ^{3}J(C,P) = 3.8, 2 CH); 120.4 (*d*, ^{3}J(C,P) = 3.8, 2 CH); 124.7 (CH); 125.0 (*d*, ^{3}J(C,P) = 2.5, CH); 125.1 (CH); 125.2 (CH); 127.3 (CH); 127.9 (*d*, ^{3}J(C,P) = 5.0, C); 128.9 (*d*, ^{3}J(C,P) = 2.5, CH); 129.0 (C); 129.5 (2 CH); 129.6 (2 CH); 131.9 (*d*, ^{3}J(C,P) = 3.8, CH); 150.3 (*d*, ^{2}J(C,P) = 10.0, C); 150.4 (*d*, ^{2}J(C,P) = 11.3, C); 153.7 (C=O). ^{31}P-NMR: 11.4. EI-MS: 488 (2, M^+), 234 (18), 170 (11), 130 (52), 129 (100), 125 (48), 98 (37), 94 (89), 77 (40), 71 (45), 51 (46), 39 (71). Anal. calc. for $C_{28}H_{29}N_{2}O_{4}P$ (488.52): C 68.84, H 5.98, N 5.73; found: C 68.70, H 5.90, N 5.67.

Diphenyl {2-[(Butylamino)carbonyl]-1,2-dihydroisoquinolin-1-yl}phosphonate (**4d**): Yield 0.50 g (97%). White powder. M.p. 133–135°. IR (KBr): 3350 (NH), 2925, 1641 (C=O), 1615, 1523, 1478, 1243 (P=O), 1207, 920, 755. ^{1}H-NMR: 0.95 (*t*, ^{3}J(H,H) = 7.0, Me); 1.39 (*m*, CH$_2$); 1.52 (*m*, CH$_2$); 3.32 (*t*, ^{3}J(H,H) = 7.1, CH$_2$N); 5.45 (br. *s*, NH); 5.94 (*d*, ^{3}J(H,H) = 5.0, CH); 5.27 (*d*, ^{2}J(P,H) = 15.0, CH); 6.71 (*d*, ^{3}J(H,H) = 7.5, CH); 6.97 (*d*, ^{3}J(H,H) = 7.6, 2 CH); 7.02 (*d*, ^{3}J(H,H) = 7.6, 2 CH); 7.09–7.15 (*m*, 3 CH); 7.24–7.33 (*m*, 7 CH). ^{13}C-NMR: 13.7 (Me); 20.1 (CH$_2$); 32.0 (CH); 42.8 (CH$_2$N); 55.1 (*d*, ^{1}J(P,C) = 153.8, C–P); 110.0 (CH); 120.2 (*d*, ^{3}J(C,P) = 5.0, 2 CH); 120.4 (*d*, ^{3}J(C,P) = 3.8, 2 CH); 124.6 (C); 125.0 (*d*, ^{3}J(C,P) = 2.4, CH); 125.1 (CH); 127.3 (CH); 127.4 (CH); 127.9 (*d*, ^{3}J(C,P) = 5.0, C); 128.9 (CH); 129.0 (CH); 129.5 (2 CH); 129.6 (2 CH); 131.8 (*d*, ^{3}J(C,P) = 3.8, CH); 150.3 (*d*, ^{2}J(C,P) = 10.0, C); 150.4 (*d*, ^{2}J(C,P) = 11.3, C); 154.6 (C=O). ^{31}P-NMR: 12.3. EI-MS: 462 (1, M^+), 234 (19), 170 (13), 130 (48), 129 (100), 99 (48), 94 (87), 77 (40), 72 (30), 57 (10), 51 (46), 45 (46), 39 (71). Anal. calc. for $C_{26}H_{27}N_{2}O_{4}P$ (462.48): C 67.52, H 5.88, N 6.06; found: C 67.39, H 5.78, N 6.10.

Diphenyl {2-[(Ethylamino)carbonyl]-1,2-dihydroisoquinolin-1-yl}phosphonate (**4e**): Yield 0.42 g (97%). White powder. M.p. 123–125°. IR (KBr): 3345 (NH), 3025, 1620 (C=O), 1619, 1582, 1468, 1293 (P=O), 1210, 915, 763. ^{1}H-NMR: 1.61 (*t*, ^{3}J(H,H) = 7.2, Me); 3.33 (*m*, CH$_2$N); 5.44 (^{2}J(P,H) = 28.0, CH); 5.92 (br. *d*, CH); 6.28 (br. *s*, NH); 6.68 (*d*, ^{3}J(H,H) = 7.5, CH); 6.95 (*d*, ^{3}J(H,H) = 8.0, 2 CH); 6.98 (*d*, ^{3}J(H,H) = 7.9, 2 CH); 7.06–7.11 (*m*, 3 CH); 7.21–7.29 (*m*, 7 CH). ^{13}C-NMR: 15.2 (Me); 36.1 (CH$_2$N); 54.9 (*d*, ^{1}J(P,C) = 155.1, C–P); 110.2 (CH); 120.2 (*d*, ^{3}J(C,P) = 4.3, 2 CH); 120.4 (*d*, ^{3}J(C,P) = 4.3, 2 CH); 124.6 (C); 124.8 (*d*, ^{3}J(C,P) = 3.0, CH); 124.9 (CH); 125.0 (CH); 127.3 (*d*, ^{4}J(C,P) = 2.5, CH); 127.9 (*d*, ^{3}J(C,P) = 5.8, C); 128.9 (CH); 129.0 (CH); 129.5 (2 CH); 129.6 (2 CH); 131.8 (*d*, ^{3}J(C,P) = 3.3, CH); 150.3 (*d*, ^{2}J(C,P) = 10.5, C); 150.5 (*d*, ^{2}J(C,P) = 10.6, C); 154.5 (C=O). ^{31}P-NMR: 13.1. EI-MS: 434 (2, M^+), 234 (18), 170 (14), 130 (46), 129 (100), 71 (49), 94 (88), 73 (30), 44 (15), 44 (30), 39 (71). Anal. calc. for $C_{24}H_{23}N_{2}O_{4}P$ (434.43): C 66.35, H 5.34, N 6.45; found: C 66.22, H 5.29, N 6.36.

Diphenyl 1,2-Dihydro-2-[(phenylamino)thioxomethyl]isoquinolin-1-yl]phosphonate (**4f**): Yield 0.48 g (96%). White powder. M.p. 152–154°. IR (KBr): 3344 (NH), 3015, 1582, 1479, 1253 (P=O), 1208, 933, 764. ^{1}H-NMR: 4.94 (*d*, ^{2}J(P,H) = 17.4, CH); 6.88 (*d*, ^{3}J(H,H) = 7.8, 2 CH); 7.05 (*t*, ^{3}J(H,H) = 7.4, CH); 7.10–7.18 (*m*, 6 CH); 6.19–6.23 (*m*, 5 CH); 7.25–7.28 (*m*, 6 CH); 7.56 (*d*, ^{3}J(H,H) = 7.19, CH); 7.92 (br. *s*, NH). ^{13}C-NMR: 54.1 (*d*, ^{1}J(P,C) = 128.5, C–P); 120.4 (*d*, ^{3}J(P,C) = 4.0, 2 CH); 120.5 (CH); 120.6 (*d*, ^{3}J(C,P) = 4.1, 2 CH); 120.7 (2 CH); 120.7 (CH); 125.1 (CH); 125.3 (2 CH); 126.4 (C); 126.5 (*d*, ^{3}J(C,P) = 3.4, CH); 127.9 (*d*, ^{4}J(C,P) = 3, CH); 128.1 (C); 128.6 (*d*, ^{3}J(C,P) = 3.9, CH); 129.5 (CH); 129.6 (CH); 129.7 (2 CH); 129.8 (2 CH); 133.6 (*d*, ^{3}J(C,P) = 6.8, CH); 133.7 (*d*, ^{3}J(C,P) = 6.7, C); 150.2 (*d*, ^{2}J(C,P) = 10.2, C); 150.3 (C=S); 150.4 (*d*, ^{2}J(C,P) = 10.5, C). ^{31}P-NMR: 12.5. EI-MS: 498 (2, M^+), 234 (23), 186 (11), 130 (50), 129 (100), 135 (50), 94 (85), 92 (38), 77 (40), 65 (44), 51 (38), 39 (65). Anal. calc. for $C_{28}H_{23}N_{2}O_{3}PS$ (498.53): C 67.46, H 4.65, N 5.62; found: C 67.20, H 4.55, N 5.55.

REFERENCES

[1] B. A. Arbusow, *Pure Appl. Chem.* **1964**, *9*, 307.
[2] S. C. Fields, *Tetrahedron* **1999**, *55*, 12237.
[3] R. Hildebrand, 'The Role of Phosphonates in Living Systems', CRC Press, Boca Raton, 1983.
[4] R. Engel, J. I. Cohen, in 'Synthesis of Carbon–Phosphorus Bonds', 2nd edn., CRC Press, 2003.
[5] S. Kobayashi, H. Kiyohara, Y. Nakamura, R. Matsubara, *J. Am. Chem. Soc.* **2004**, *126*, 6558.
[6] I. Yavari, Z. Hossaini, A. Alizadeh, *Monatsh. Chem.* **2006**, *137*, 1083.
[7] A. Alizadeh, I. Yavari, *Mendeleev Commun.* **2005**, *15*, 154.

[8] I. Yavari, M. H. Mosslemin, A. R. Montahaei, *J. Chem. Res., Synop.* **1998**, 576.
[9] R. Huisgen, M. Morikawa, K. Herbig, E. Brunn, *Chem. Ber.* **1967**, *100*, 1094.
[10] H. J. Dillinger, G. Fengler, D. Schumann, E. Winterfeldt, *Tetrahedron* **1974**, *30*, 2561.

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