

Formation of Phosphorylated 3*H*-Pyrroles from *Nef*–Isocyanide–*Perkow* Adducts and Tosylmethyl Isocyanide

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Imidoyl chlorides, generated from isocyanides and acyl chlorides, react with trialkyl phosphites, in a *Perkow*-type reaction, to afford 3-(alkylimino)-2-[(dialkyloxyphosphoryl)oxy]acrylates, which undergo a smooth reaction with tosylmethyl isocyanide (TsMIC) to furnish 4-(alkylamino)-3-[(dialkyloxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3*H*-pyrrole-3-carboxylates in moderate-to-good yields.

Introduction. – Sequential one-pot transformations offer significant advantages over conventional linear-step syntheses, by reducing time and saving energy, thus resulting in both economic and environmental benefits [1–4]. Multicomponent synthesis has been established as a valuable tool to the pharmaceutical industry for construction of low-molecular-weight compound libraries through combinatorial strategies and parallel synthesis [5–7]. Although (*p*-toluenesulfonyl)methyl isocyanide (=1-[(isocyanomethyl)sulfonyl]-4-methylbenzene; TsMIC) is a versatile and widely applicable reagent that constitutes a functionalized building block [8] bearing an active CH₂ group apart from its inherent advantage of possessing also an isocyanide functionality, which can serve as a handle for further manipulation, the possibility of its use in multicomponent reactions has not been widely appreciated. TsMIC has most commonly been used in heterocyclic ring construction [9][10], in particular, of oxazole and pyrrole moieties, but comparatively rarely in multicomponent reactions [11][12]. Since the reaction between imines and TsMIC in basic media is a trusted method for the synthesis of 1,5-disubstituted imidazoles [13], we speculated that formation of functionalized 3*H*-pyrroles *via* cyclizations of *Nef*–isocyanide–*Perkow* products and TsMIC would be possible, *via* a sequential one-pot transformation.

As part of our interest in the development of new routes in heterocyclic synthesis [14–18], we studied the reaction between ketenimines and TsMIC in basic solution. This reaction provided new 4-(alkylamino)-3-[(dialkyloxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3*H*-pyrrole-3-carboxylates.

Results and Discussion. – Initially, we studied the reaction of ethyl 2-chloro-2-oxoacetate (**1a**), cyclohexyl isocyanide (**2a**), P(OMe)₃ (**3a**), and TsMIC (**4**) in the presence of common bases at room temperature in different solvent systems, and the results are compiled in *Table 1*. The desired product **5a** could be obtained in 23–53% yield using THF, CH₂Cl₂, acetone, EtOH, and MeCN as solvent, but MeCN afforded the highest yield (*Table 1*, *Entry 2*). Common bases such as Et₃N, DBU (=1,8-

Table 1. Reaction of Ethyl 2-Chloro-2-oxoacetate (**1a**), Cyclohexyl Isocyanide (**2a**), Trimethyl Phosphite (**3a**), and TsMIC in the Presence of a Base^a

Entry	Solvent	Base	Time [h] ^b	Yield [%] ^c of 5a
1	MeCN	Et ₃ N	7	35
2	MeCN	DBU	4	53
3	MeCN	KOH	7	23
4	MeCN	K ₂ CO ₃	7	25
5	MeCN	NaHCO ₃	7	38
6	THF	DBU	7	24
7	EtOH	DBU	7	38
8	CH ₂ Cl ₂	DBU	7	27
9	Acetone	DBU	7	32

^a) General conditions: **1** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), TsMIC (**4**; 1 mmol), and base (1 mmol).
^b) Reaction time for consumption of all starting materials. ^c) Yields of isolated product.

diazabicyclo[5.4.0]undec-7-ene), K₂CO₃, NaHCO₃, and KOH can catalyze this reaction with low-to-moderate yields (Table 1, Entries 1–9). However, DBU turned out to be the optimal catalyst (Table 1, Entry 2).

With the suitable reaction conditions in hand, we next explored the protocol with different alkyl 2-chloro-2-oxoacetates **1**, isocyanides **2**, trialkyl phosphites **3**, and TsMIC (**4**) in the presence of DBU in MeCN. As shown in Table 2, the reaction

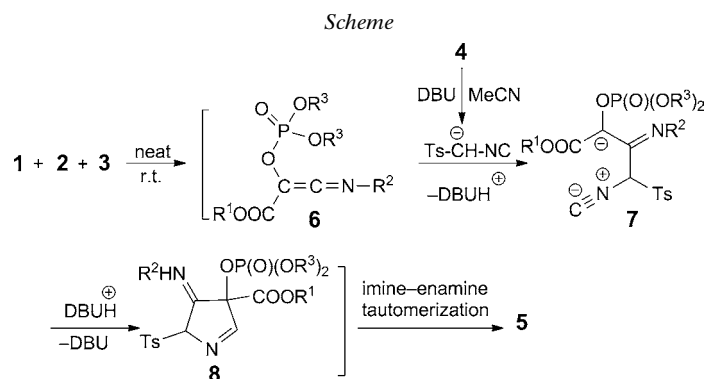
Table 2. Synthesis of Functionalized 3-[(Dialkyloxyphosphoryl)oxy]-3H-pyrrole-3-carboxylates **5**

Entry	R ¹	R ²	R ³	Yield [%]
1	Et	Cyclohexyl	Me	5a (53)
2	Me	^t Bu	Me	5b (57)
3	Me	^t Bu	Et	5c (48)
4	Et	^t Bu	Me	5d (45)
5	Et	Cyclohexyl	Et	5e (59)
6	Me	Cyclohexyl	Et	5f (55)
7	Me	Cyclohexyl	Me	5g (60)

afforded the corresponding 4-(alkylamino)-3-[(dialkyloxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3*H*-pyrrole-3-carboxylates **5** in 45–60% yields.

The structures of compounds **5a–5g** were deduced from their IR, and ¹H- and ¹³C-NMR data. For example, the ¹H-NMR spectrum of **5a**, exhibited two *singlets* for Me (2.32 ppm) and HC=N (7.57 ppm), two *doublets* for MeO (3.67, (³*J*(H,P) = 14.1) and 3.75 ppm (³*J*(H,P) = 14.1)), along with characteristic signals for the rest of H-atoms. The ¹H-decoupled ¹³C-NMR spectrum of **5a** showed 20 distinct resonances in agreement with the proposed structure. The ¹H- and ¹³C-NMR spectra of compounds **5b–5g** are similar to those of **5a**, except for the substituents on the pyrrole ring, which show characteristic signals in the appropriate regions of the spectra.

Although the detailed mechanism of this reaction remains to be clarified, a plausible mechanism for the formation of compounds **5** is proposed in the *Scheme*. The addition of isocyanides to acyl chlorides (*Nef*-isocyanide reaction) leads to imidoyl chlorides, which can later react with trialkyl phosphites to afford ketenimine intermediates **6** in a *Perkow*-type reaction [19]. It is conceivable that formation of intermediate **7** takes place through a nucleophilic attack of the base-activated TsMIC at **6**. Intramolecular *5-endo-dig* ring formation of **7** affords intermediate **8**, which is converted to **5** by imine–enamine tautomerization.



In summary, imidoyl chlorides react with trialkyl phosphites, in a *Perkow*-type reaction, to afford intermediate 3-(alkylimino)-2-[(dialkyloxyphosphoryl)oxy]acrylates, which undergo a smooth reaction with TsMIC to afford 4-(alkylamino)-3-[(dialkyloxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3*H*-pyrrole-3-carboxylates in moderate-to-good yields. The mild and simple reaction conditions renders this transformation suitable for synthesis of functionalized 3-[(dialkyloxyphosphoryl)oxy]-3*H*-pyrrole-3-carboxylates.

Experimental Part

General. All chemicals were obtained commercially and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1} . ¹H- and ¹³C-NMR Spectra: *Bruker DRX-500 Avance* instrument at 500.1 and 125.7 MHz, resp.; δ in ppm, *J* in Hz. MS:

Finnigan-MAT-8430 spectrometer; at 70 eV; in m/z (rel. %). Elemental analyses: Vario EL III CHNOS elemental analyzer.

General Procedure for the Synthesis of Compound 7. A mixture of **1** (1 mmol) and **2** (1 mmol) was stirred at r.t. for 10 min. Then, **3** (1 mmol) was added. After stirring the mixture for 5 min, a soln. of TsMIC (1.0 mmol) and DBU (1.0 mmol) in MeCN (5 ml) was added in one portion. After 4 h, the solvent was removed under reduced pressure, and the residue was purified by SiO₂ (Merck 230–240 mesh) column chromatography (hexane/AcOEt 2:1).

Ethyl 4-(Cyclohexylamino)-3-[(dimethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5a). Pale-yellow oil. Yield: 0.27 g (53%). IR (KBr): 3484 (NH), 1755 (C=O), 1284 (SO₂), 1040 (C–O). ¹H-NMR: 1.18 (t, ³J = 7.1, Me); 1.20–2.02 (m, 5 CH₂); 2.32 (s, Me); 3.78–3.93 (m, CH); 3.67 (d, ³J(H,P) = 14.1, Me); 3.75 (d, ³J(H,P) = 14.1, Me); 7.00 (d, ³J = 7.0, NH); 7.24 (d, ³J = 8.1, 2 CH); 7.57 (s, HC=N); 7.92 (d, ³J = 8.1, 2 CH). ¹³C-NMR: 13.8 (Me); 21.4 (Me); 24.7; 25.5; 25.6; 34.3; 34.8 (5 CH₂); 54.6 (d, ²J(C,P) = 5.7, Me); 54.7 (d, ²J(C,P) = 5.7, Me); 56.6 (CH); 62.7 (CH₂); 66.7 (d, ²J(C,P) = 5.0, COP); 127.2 (C); 128.1 (2 CH); 129.5 (2 CH); 137.1 (CH); 138.0 (C); 138.9 (C); 144.2 (C); 166.9 (d, ³J(C,P) = 5.5, C=O). EI-MS: 514 (5, M⁺), 508 (11), 469 (32), 368 (12), 256 (25), 236 (24), 213 (19), 185 (15), 136 (55), 111 (39), 97 (56), 81 (73), 60 (57). Anal. calc. for C₂₂H₃₁N₂O₈PS (514.15): C 51.35, H 6.07, N 5.44; found: C 51.03, H 5.98, N 5.38.

Methyl 4-[(tert-Butyl)amino]-3-[(dimethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5b). Pale-yellow oil. Yield: 0.27 g (57%). IR (KBr): 3427 (NH), 1755 (C=O), 1270 (SO₂), 1043 (C–O). ¹H-NMR: 1.34 (s, tBu); 2.33 (s, Me); 3.57 (d, ³J(H,P) = 14.3, Me); 3.63 (s, Me); 3.71 (d, ³J(H,P) = 14.3, Me); 7.26 (d, ³J = 8.2, 2 CH); 7.66 (s, HC=N); 7.80 (s, NH); 7.92 (d, ³J = 8.2, 2 CH). ¹³C-NMR: 21.6 (Me); 30.7 (Me₃C); 51.6 (Me₃C); 54.4 (d, ²J(C,P) = 3.0, Me); 53.4 (COOMe); 55.2 (d, ²J(C,P) = 3.0, Me); 66.6 (d, ²J(C,P) = 4.1, COP); 127.7 (C); 128.3 (2 CH); 129.0 (2 CH); 137.9 (CH); 139.6 (C); 140.1 (C); 144.1 (C); 166.5 (d, ³J(C,P) = 5.4, C=O). EI-MS: 474 (4, M⁺), 460 (5), 410 (7), 386 (9), 359 (11), 310 (10), 277 (16), 251 (17), 236 (43), 216 (49), 187 (91), 172 (100), 158 (38), 139 (63), 111 (36), 91 (82), 71 (56), 57 (89). Anal. calc. for C₁₉H₂₇N₂O₈PS (474.12): C 48.10, H 5.74, N 5.90; found: C 48.25, H 5.68, N 5.84.

Methyl 4-[(tert-Butyl)amino]-3-[(diethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5c). Pale-yellow oil. Yield: 0.25 g (48%). IR (KBr): 3305 (NH), 1758 (C=O), 1272 (SO₂), 1035 (C–O). ¹H-NMR: 1.15–1.18 (m, 2 Me); 1.33 (s, tBu); 2.36 (s, Me); 3.84 (s, COOMe); 4.12–4.20 (m, 2 CH₂); 7.08 (s, NH); 7.27 (d, ³J = 8.0, 2 CH); 7.70 (s, HC=N); 7.88 (d, ³J = 8.0, 2 CH). ¹³C-NMR: 16.0 (d, ³J(C,P) = 6.0, Me); 16.4 (d, ³J(C,P) = 6.0, Me); 21.6 (Me); 28.5 (Me₃C); 51.9 (Me₃C); 53.2 (CO₂Me); 65.7 (d, ²J(C,P) = 5.9, COP); 64.8 (d, ²J(C,P) = 2.9, CH₂); 64.9 (d, ²J(C,P) = 2.9, CH₂); 122.8 (C); 127.9 (2 CH); 129.7 (2 CH); 137.6 (CH); 138.8 (C); 143.0 (C); 144.2 (C); 166.0 (d, ³J(C,P) = 4.1, C=O). EI-MS: 502 (4, M⁺), 492 (5), 362 (8), 355 (10), 270 (15), 253 (23), 226 (96), 199 (63), 171 (19), 155 (42), 138 (71), 99 (72), 58 (51). Anal. calc. for C₂₁H₃₁N₂O₈PS (502.15): C 50.19, H 6.22, N 5.57; found: C 50.57, H 6.17, N 5.49.

Ethyl 4-[(tert-Butyl)amino]-3-[(dimethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5d). Pale-yellow oil. Yield: 0.20 g (45%). IR (KBr): 3417 (NH), 1753 (C=O), 1278 (SO₂), 1044 (C–O). ¹H-NMR: 1.20 (t, ³J = 7.0, Me); 1.31 (s, tBu); 2.32 (s, Me); 3.21–3.36 (m, CH₂); 3.51 (d, ³J(H,P) = 14.0, Me); 3.68 (d, ³J(H,P) = 14.0, Me); 7.28 (d, ³J = 8.3, 2 CH); 7.60 (s, NH); 7.71 (s, HC=N); 8.31 (d, ³J = 8.3, 2 CH). ¹³C-NMR: 14.6 (Me); 21.6 (Me); 28.5 (Me₃C); 51.4 (Me₃C); 52.5 (d, ²J(C,P) = 3.1, Me); 55.1 (d, ²J(C,P) = 3.1, Me); 58.1 (CH₂); 65.1 (d, ²J(C,P) = 5.8, COP); 127.6 (C); 128.2 (2 CH); 129.4 (2 CH); 137.6 (CH); 138.2 (C); 138.5 (C); 142.9 (C); 165.3 (d, ³J(C,P) = 6.1, C=O). EI-MS: 488 (3, M⁺), 473 (10), 415 (9), 401 (13), 343 (11), 319 (14), 265 (93), 249 (42), 172 (46), 139 (64), 123 (42), 91 (100), 65 (57), 51 (17). Anal. calc. for C₂₀H₂₉N₂O₈PS (488.13): C 49.17, H 5.98, N 5.73; found: C 49.59, H 5.91, N 5.68.

Ethyl 4-(Cyclohexylamino)-3-[(diethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5e). Pale-yellow oil. Yield: 0.32 g (59%). IR (KBr): 3484 (NH), 1756 (C=O), 1283 (SO₂), 1041 (C–O). ¹H-NMR: 1.15–1.31 (m, 3 Me); 1.21–1.98 (m, 5 CH₂); 2.35 (s, Me); 3.76–3.85 (m, CH); 4.00–4.25 (m, 3 CH₂); 7.01 (d, ³J = 6.8, NH); 7.25 (d, ³J = 8.2, 2 CH); 7.57 (s, HC=N); 7.94 (d, ³J = 8.2, 2 CH). ¹³C-NMR: 14.0 (Me); 15.9 (d, ³J(C,P) = 6.9, Me); 16.1 (d, ³J(C,P) = 6.9, Me); 21.5 (Me); 24.8, 25.6, 25.6, 34.4, 34.8 (5 CH₂); 56.6 (CH); 53.6 (CH₂); 64.4 (d, ²J(C,P) = 5.6, CH₂); 64.5 (d, ²J(C,P) = 5.6,

CH₂); 66.0 (*d*, ²*J*(C,P) = 4.3, COP); 127.5 (C); 128.1 (2 CH); 129.5 (2 CH); 137.1 (CH); 138.1 (C); 138.8 (C); 144.1 (C); 167.2 (*d*, ³*J*(C,P) = 5.6, C=O). EI-MS: 542 (5, *M*⁺), 387 (100), 368 (8), 352 (10), 317 (22), 271 (25), 243 (18), 150 (16), 133 (17), 110 (10), 83 (19), 57 (5). Anal. calc. for C₂₄H₃₅N₂O₈PS (542.18): C 53.13, H 6.50, N 5.16; found: C 53.51, H 6.44, N 5.23.

Methyl 4-(Cyclohexylamino)-3-[(diethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5f). Pale-yellow oil. Yield: 0.29 g (55%). IR (KBr): 3479 (NH), 1755 (C=O), 1284 (SO₂), 1040 (C–O). ¹H-NMR: 1.27–1.37 (*m*, 2 Me); 1.23–2.00 (*m*, 5 CH₂); 2.34 (*s*, Me); 3.69–3.77 (*m*, CH); 4.05 (*s*, COOMe); 4.10–4.21 (*m*, 2 CH₂); 7.02 (*d*, ³*J* = 6.9, NH); 7.24 (*d*, ³*J* = 8.1, 2 CH); 7.55 (*s*, HC=N); 7.93 (*d*, ³*J* = 8.1, 2 CH). ¹³C-NMR: 16.6 (*d*, ³*J*(C,P) = 6.7, Me); 16.9 (*d*, ³*J*(C,P) = 6.7, Me); 22.6 (Me); 25.6, 25.6, 32.6, 34.5, 34.7 (5 CH₂); 53.6 (Me); 56.7 (CH); 64.4 (*d*, ²*J*(C,P) = 5.6, CH₂); 64.6 (*d*, ²*J*(C,P) = 5.6, CH₂); 64.9 (*d*, ²*J*(C,P) = 5.7, COP); 127.4 (C); 127.5 (2 CH); 129.8 (2 CH); 137.0 (CH); 138.0 (C); 138.2 (C); 144.2 (C); 167.6 (*d*, ³*J*(C,P) = 5.7, C=O). EI-MS: 528 (6, *M*⁺), 483 (7), 469 (43), 373 (100), 315 (8), 293 (32), 251 (27), 155 (28), 127 (16), 99 (32), 83 (31), 56 (29). Anal. calc. for C₂₃H₃₃N₂O₈PS (528.17): C 52.26, H 6.29, N 5.30; found: C 52.54, H 6.22, N 5.23.

Methyl 4-(Cyclohexylamino)-3-[(dimethoxyphosphoryl)oxy]-5-[(4-methylphenyl)sulfonyl]-3H-pyrrole-3-carboxylate (5g). Pale-yellow oil. Yield: 0.30 g (60%). IR (KBr): 3436 (NH), 1751 (C=O), 1280 (SO₂), 1030 (C–O). ¹H-NMR: 1.19–1.86 (*m*, 5 CH₂); 2.37 (*s*, Me); 3.47 (*d*, ³*J*(H,P) = 13.8, Me); 3.76 (*d*, ³*J*(H,P) = 13.8, Me); 3.85 (*s*, COOMe); 3.86–3.93 (*m*, CH); 7.05 (*d*, ³*J* = 8.7, NH); 7.28 (*d*, ³*J* = 8.2, 2 CH); 7.59 (*s*, HC=N); 7.96 (*d*, ³*J* = 8.2, 2 CH). ¹³C-NMR: 21.6 (Me); 24.8, 25.6, 25.6, 34.4, 34.8 (5 CH₂); 53.2 (CH); 54.7 (*d*, ²*J*(C,P) = 5.6, Me); 54.8 (*d*, ²*J*(C,P) = 5.7, Me); 56.7 (Me); 66.3 (*d*, ²*J*(C,P) = 4.2, COP); 127.2 (C); 128.2 (2 CH); 129.6 (2 CH); 137.1 (CH); 137.9 (C); 139.0 (C); 144.3 (C); 167.6 (*d*, ³*J*(C,P) = 5.6, C=O). EI-MS: 500 (7, *M*⁺), 469 (23), 387 (27), 373 (72), 345 (69), 293 (21), 242 (78), 198 (100), 166 (91), 127 (46), 110 (47), 84 (51), 58 (36). Anal. calc. for C₂₁H₂₉N₂O₈PS (500.14): C 50.39, H 5.84, N 5.60; found: C 50.02, H 5.76, N 5.65.

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