# The Triphenyl Phosphite–Chlorine Reagent in the Synthesis of Pyrroles from *N*-Allylamides

Alberto Spaggiari, Daniele Vaccari, Paolo Davoli, Fabio Prati*

Dipartimento di Chimica, Università di Modena e Reggio Emilia, via Campi 183, 41100 Modena, Italy
Fax +39(059)373543; E-mail: prati.fabio@unimore.it

*Received 6 September 2005; revised 10 November 2005*

**Abstract:** A novel application of $(PhO)_3P–Cl_2$ chemistry to the synthesis of 2-substituted and 2,3-disubstituted pyrroles from *N*-allylamides is illustrated. A mild procedure is used to generate the imino chloride intermediates, which are subsequently cyclized to pyrroles. The products are smoothly obtained in moderate to good overall yields.

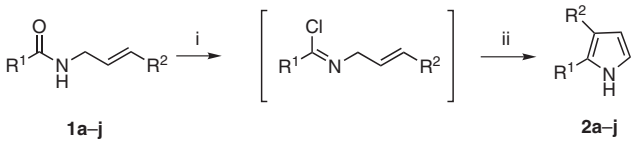
**Key words:** triphenyl phosphite, chlorine, pyrroles, allylamides, cyclizations

Since its first appearance in 1879,[1] which was followed five years later by the more famous and general Knorr approach,[2] the construction of the pyrrole core has always featured as a key topic in heterocyclic chemistry. In fact, molecules containing the pyrrole skeleton as a structural motif are still being used for a wide range of pharmaceutical and industrial applications. Hence, much effort has been devoted to the chemistry of substituted pyrroles, which are endowed with anti-inflammatory and analgesic properties[3] and also represent a key unit in several biologically active compounds.[4] Accordingly, a variety of synthetic routes towards their synthesis have been developed.[5]

In the course of our work with the halogenating reagent $(PhO)_3P–Cl_2$ ($TPPCl_2$) we had the opportunity to explore the reactivity of imino chlorides as easily formed versatile intermediates in the deacylation of amides to amines[6] and for the cyclocondensation to β-carbolines and isoquinolines.[7] Compared to literature methods our $TPPCl_2$-based access to imino chlorides has resulted in easier experimental protocols as these synthetic intermediates can be smoothly prepared under mild conditions from the corresponding amides.

Therefore, as part of our ongoing investigations on the synthetic potential of this reagent, we decided to assess whether $TPPCl_2$ could be successfully applied to the synthesis of small-sized heterocycles such as pyrroles. In particular, we reasoned that allylamides could be used as convenient substrates for an intramolecular cyclization to pyrroles via imino chlorides (Scheme 1). Allyl derivatives have been exploited in the past for the synthesis of substituted pyrroles, even though severe conditions and lengthy procedures were generally employed.[1,5a,8] In addition, such an approach would also probe the validity of our $TPPCl_2$-promoted imino chloride protocol[6a] and broaden its synthetic application. To this end, a representative set of diversely substituted *N*-allylamides was chosen and subjected to halogenation with $TPPCl_2$, followed by treatment with potassium *tert*-butoxide to achieve intramolecular cyclization.

*N*-Allylamides **1a–j** (Table 1) were treated with freshly prepared $TPPCl_2$ in toluene at –25 °C in the presence of triethylamine[6a] to afford the corresponding imino chlorides. After rapid centrifugation to remove triethylamine hydrochloride, the solvent was changed to THF and the solution was used as such for the next cyclization step. Treatment with potassium *tert*-butoxide in anhydrous DMF at 0 °C resulted in a sudden color change to violet, which indicated that the cyclization was taking place successfully. The dark coloration persisted throughout the reaction, which reached completion within 30 minutes (for derivative **1f** the reaction mixture remained colorless during the cyclization step). Extraction followed by chromatographic purification allowed the removal of triphenyl phosphate and phenol,[9] and afforded pyrroles **2a–j** in moderate to good yields (25–78%). The results are summarized in Table 1.



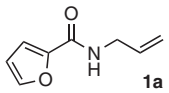
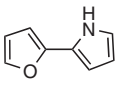
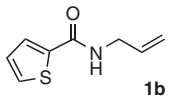
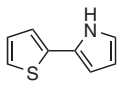
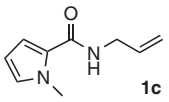
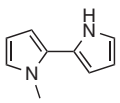
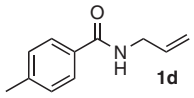
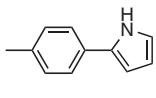
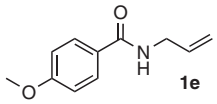
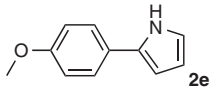
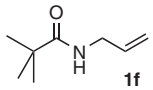
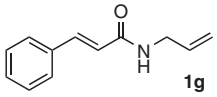
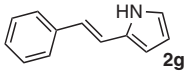
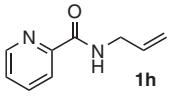
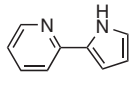
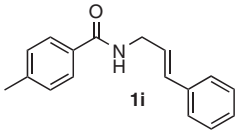
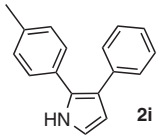
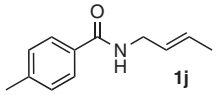
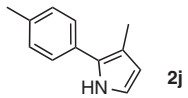

1a–j 2a–j

**Scheme 1** General route from *N*-allylamides **1** to pyrroles **2**. *Reagents and conditions*: (i) $(PhO)_3P–Cl_2$, $Et_3N$, toluene, –25 °C to r.t.; (ii) *t*-BuOK, DMF–THF, 0 °C.

The presence of aryl or heteroaryl groups such as substituted phenyl rings, N-, O-, or S-containing heterocycles were found to be compatible with the reaction conditions. The highest yields were observed with *N*-allylamides bearing electron-rich pentatomic heterocyclic groups, such as furoyl-, thiophenyl-, and pyrrolylamides **1a–c**, whereas pyridylamide **1h** bearing an electron-deficient heteroaromatic moiety gave only a modest result. Such dual behavior, though a priori foreseeable, is a bit surprising in its magnitude, and would suggest a remarkable electronic influence by the pre-existing heterocyclic ring, which may affect the stability of the chloroiminoyl carbon atom and, consequently, its tendency to undergo intramolecular attack.

**SYNTHESIS** 2006, No. 6, pp 0995–0998
Advanced online publication: 27.02.2006
DOI: 10.1055/s-2006-926365; Art ID: T12005SS

**Table 1** Cyclization Products and Results

| Amide | Pyrrole | Yield (%) |
|---|---|---|
|  1a |  2a | 78 |
|  1b |  2b | 65 |
|  1c |  2c | 71 |
|  1d |  2d | 65 |
|  1e |  2e | 60 |
|  1f |  2f | 32 |
|  1g |  2g | 25 |
|  1h |  2h | 29 |
|  1i |  2i | 52 |
|  1j |  2j | 58 |

Inevitably, application of the method is restricted to allylamides lacking enolizable H atoms. Pivaloylamide **1f** was cyclized, albeit in moderate yield, which may be also due to the high volatility of pyrrole **2f**. In the case of cinnamoyl amide **1g**, the low yield might be explained by a competing conjugate addition under the cyclization conditions, since no inherent incompatibility of the cinnamoyl residue with $TPPCl_2$ can be invoked.[6a] Therefore, $R^1$ can be represented either by an aromatic ring or a quaternary carbon atom, whereas no particular limitations are required for $R^2$. *N*-Cinnamyl and crotyl amides (**1i** and **1j**, respectively), for instance, were satisfactorily converted into the corresponding 2,3-disubstituted pyrroles (**2i** and **2j**).

Similar results were described by Steglich,[5a] albeit on a narrower set of compounds, using phosgene in DMF–toluene at 40–50 °C for the preparation of the imino chloride intermediates, which were subsequently cyclized to 2-aryl and 2-heteroarylpyrroles with potassium *tert*-butoxide in DMF. Although overall yields were comparable, the use of $TPPCl_2$ allows milder reaction conditions and offers a somewhat greater ease of handling with respect to the highly toxic phosgene.

In conclusion, our $TPPCl_2$-based methodology represents the mildest route available in the literature to access 2-substituted and 2,3-disubstituted pyrroles from allylamides. The short reaction times, the low temperatures employed, and the lack of intermediate purifications render this approach a valuable option when targeting substituted pyrroles.

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX 200 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm downfield from TMS as internal standard and coupling constants (*J*) are given in Hz. MS were determined on a Finnigan MAT SSQ A (EI, 70 eV), while elemental analyses were performed by means of a Carlo Erba Elemental Analyzer 1110. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. All organic solvents were dried according to standard methods and glassware was oven-dried at 120 °C for 4 h and assembled under an Ar stream. PE used had a bp range 40–60 °C.

### *N*-Allylamides 1a–j

*N*-Allylamides **1a–j** were prepared by reacting allylamine with a suitable acyl chloride in the presence of $Et_3N$ in refluxing $CH_2Cl_2$, according to standard procedures.[10] All compounds gave satisfactory elemental analyses and had spectroscopic properties in perfect agreement with literature data.

### Cyclization to Pyrroles 2a–j; General Procedure

$Cl_2$ was bubbled through a glass septum into a cold solution (–25 °C) of $(PhO)_3P$ (1.1 mmol) in anhyd toluene (20 mL) until a bright yellow color appeared. Upon further addition of a few drops of $(PhO)_3P$ the color faded to pale yellow. The amide **1** (1 mmol) and anhyd $Et_3N$ (1.15 mmol) were then added. The mixture was stirred for 3 h and left to warm to r.t. After centrifugation, the mixture was washed with anhyd THF (3 × 10 mL), the combined organic layers were concentrated under reduced pressure, and the sticky residue was finally dissolved in anhyd THF (20 mL). The solution thus obtained was added dropwise to a cooled (0 °C) suspension of *t*-BuOK (8 mmol) in anhyd DMF (30 mL). The reaction mixture immediately turned dark purple to violet in color. After stirring for 30 min at the same temperature, the dark solution was poured into ice-cold water (400 mL) and extracted with $Et_2O$ (3 × 150 mL). The combined organic phases were washed with 10% NaOH (3 × 70 mL), dried over $Na_2SO_4$, and evaporated in vacuo to afford an oily residue, which was purified by column chromatography on silica gel (PE–$Et_2O$, 80:20).

### 2-Furan-2-yl-1*H*-pyrrole (2a)

Black crystals; mp 44 °C.

IR (KBr): 2932, 3116, 3401 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 6.28 (dd, *J* = 2.7, 6.1 Hz, 1 H, H-4), 6.36 (d, *J* = 3.3 Hz, 1 H, H-3′), 6.43–6.48 (m, 2 H, H-3, H-4′), 6.81 (dt, *J* = 1.5, 2.7 Hz, 1 H, H-5), 7.37 (d, *J* = 1.8 Hz, 1 H, H-5′), 8.59 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 102.2, 105.3, 109.7, 111.4, 118.2, 140.3, 148.4.

MS (EI): *m*/*z* (%) = 133 ($M^+$, 100), 104 (85), 78 (17).

Anal. Calcd for $C_8H_7NO$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.25; H, 5.32; N, 10.38.

**2-Thiophen-2-yl-1*H*-pyrrole (2b)**
Fine grey powder; mp 78–80 °C.

IR (KBr): 2932, 3366 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 6.30 (dd, *J* = 2.6, 6.0 Hz, 1 H, H-4), 6.46 (dt, *J* = 1.5, 2.6 Hz, 1 H, H-3), 6.82 (dt, *J* = 1.5, 2.6 Hz, 1 H, H-5), 7.01–7.07 (m, 2 H, H-3′, H-4′), 7.17 (dd, *J* = 2.4, 3.8 Hz, 1 H, H-5′), 8.31 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 106.8, 110.0, 118.5, 120.9, 122.7, 126.7, 127.6, 136.3.

MS (EI): *m*/*z* (%) = 149 ($M^+$, 100), 121 (22), 104 (15).

Anal. Calcd for $C_8H_7NS$: C, 64.39; H, 4.73; N, 9.39; S, 21.49. Found: C, 64.55; H, 4.81; N, 9.20; S, 21.50.

**1-Methyl-1*H*,1′*H*-[2,2′]bipyrrole (2c)**
Black crystals; mp 44–45 °C.

IR (KBr): 2924, 3112, 3362 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 3.74 (s, 3 H, $NCH_3$), 6.25 (d, *J* = 2.2 Hz, 1 H, H-4), 6.28–6.33 (m, 2 H, H-3, H-4′), 6.36 (dd, *J* = 2.7, 6.0 Hz, 1 H, H-3′), 6.74 (d, *J* = 2.2 Hz, 1 H, H-5), 6.84 (dt, *J* = 1.5, 2.7 Hz, 1 H, H-5′), 8.19 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 35.1, 106.8, 107.0, 107.6, 109.3, 117.7, 123.0, 124.4, 127.2.

MS (EI): *m*/*z* (%) = 146 ($M^+$, 100), 131 (23), 118 (19), 104 (16).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.80; H, 6.92; N, 19.12.

**2-*p*-Tolyl-1*H*-pyrrole (2d)**
Fine ivory powder; mp 152–153 °C.

IR (KBr): 3103, 3393 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 2.39 (s, 3 H, $CH_3$), 6.32 (dd, *J* = 1.5, 2.7 Hz, 1 H, H-4), 6.52 (dq, *J* = 2.7, 6.0 Hz, 1 H, H-3), 6.85 (dt, *J* = 1.5, 2.7 Hz, 1 H, H-5), 7.20 (d, *J* = 8.1 Hz, 2 H, ArH), 7.40 (d, *J* = 8.1 Hz, 2 H, ArH), 8.40 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 21.1, 105.4, 110.0, 118.4, 123.9, 129.6, 130.1, 132.3, 135.9.

MS (EI): *m*/*z* (%) = 157 ($M^+$, 100), 128 (10).

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.90; H, 7.10; N, 9.00.

**2-(4-Methoxyphenyl)-1*H*-pyrrole (2e)**
Pale green solid; mp 145–147 °C.

IR (KBr): 2836, 2959, 3393, 3441 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 3.84 (s, 3 H, $OCH_3$), 6.30 (dd, *J* = 2.7, 6.0 Hz, 1 H, H-4), 6.43 (dq, *J* = 1.5, 2.7 Hz, 1 H, H-3), 6.83 (dt, *J* = 1.5, 2.7 Hz, 1 H, H-5), 6.93 (d, *J* = 8.9 Hz, 2 H, ArH), 7.42 (d, *J* = 8.9 Hz, 2 H, ArH), 8.41 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 55.3, 104.9, 109.9, 114.4, 118.2, 125.3, 126.0, 132.1, 158.3.

MS (EI): *m*/*z* (%) = 173 ($M^+$, 97), 158 (100), 130 (30).

Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.50; H, 6.50; N, 8.01.

**2-*tert*-Butyl-1*H*-pyrrole (2f)**
Mint-scented waxy reddish-brown crystals; mp 40–42 °C.

IR (KBr): 2872, 2967, 3404 (br) $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 1.47 [s, 9 H, $C(CH_3)_3$], 6.13 (dq, *J* = 1.6, 2.7 Hz, 1 H, H-4), 6.31 (dd, *J* = 2.7, 5.9 Hz, 1 H, H-3), 6.81 (dt, *J* = 1.6, 2.7 Hz, 1 H, H-5), 8.10 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 30.7, 31.4, 102.5, 107.9, 116.2, 142.0.

MS (EI): *m*/*z* (%) = 124 ($[M + 1]^+$, 91), 108 (100), 68 (76), 57 (52).

Anal. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.97. Found: C, 78.00; H, 10.04; N, 11.89.

**2-Styryl-1*H*-pyrrole (2g)**
Green-brown fine powder; mp 123–124 °C.

IR (KBr): 2932, 3428 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 6.38 (s, 1 H, H-4), 6.54 (s, 1 H, H-3), 6.68 (d, *J* = 16.5 Hz, 1 H, =CH), 6.82 (s, 1 H, H-5), 7.01 (d, *J* = 16.5 Hz, 1 H, =CHPh), 7.36 (m, 5 H, ArH), 8.34 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 109.2, 110.0, 119.0, 119.1, 123.4, 125.8, 126.2, 126.9, 128.7, 128.9.

MS (EI): *m*/*z* (%) = 169 ($M^+$, 100), 168 (87), 143 (72), 115 (48).

Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.17; H, 6.65; N, 8.33.

**2-(1*H*-Pyrrol-2-yl)pyridine (2h)**
Brown solid; mp 90–91 °C.

IR (KBr): 3410 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 6.31 (dt, *J* = 2.6, 3.6 Hz, 1 H, H-4′), 6.74–6.79 (m, 1 H, H-3′), 6.87–6.95 (m, 2 H, H-3, H-5′), 7.03 (dd, *J* = 2.0, 5.5 Hz, 1 H, H-5), 7.20–7.28 (m, 1 H, H-4), 8.33 (dd, *J* = 0.5, 5.5 Hz, 1 H, H-6), 10.21 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 109.2, 110.6, 118.6, 120.3, 120.6, 129.6, 129.9, 149.1, 156.4.

MS (EI): *m*/*z* (%) = 144 ($M^+$, 100).

Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.74; H, 5.73; N, 19.37.

**3-Phenyl-2-*p*-tolyl-1*H*-pyrrole (2i)**
Grey powder; mp 123–124 °C.

IR (KBr): 3029, 3336 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 2.39 (s, 3 H, $CH_3$), 6.46 (t, *J* = 2.7 Hz, 1 H, H-4), 6.88 (t, *J* = 2.7 Hz, 1 H, H-3) 7.12–7.44 (m, 9 H, ArH), 8.21 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 21.2, 110.9, 117.8, 121.6, 125.6, 127.5, 128.2, 128.4, 129.4, 130.5, 132.1, 136.5, 136.8.

MS (EI): *m*/*z* (%) = 233 ($M^+$, 100), 217 (15).

Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.45; H, 6.53; N, 5.99.

**3-Methyl-2-*p*-tolyl-1*H*-pyrrole (2j)**
Reddish-grey glittering solid; mp 65–67 °C.

IR (KBr): 2862, 2923, 3423 $cm^{-1}$.

$^1H$ NMR (200 MHz): δ = 2.29 (s, 3 H, $CH_3$), 2.40 (s, 3 H, *p*-$CH_3$), 6.17 (s, 1 H, H-4), 6.77 (s, 1 H, H-5), 7.23 (d, *J* = 8.1 Hz, 2 H, ArH), 7.34 (d, *J* = 8.1 Hz, 2 H, ArH), 8.11 (br s, 1 H, NH).

$^{13}C$ NMR (50 MHz): δ = 12.4, 21.1, 112.0, 116.8, 126.3, 126.4, 129.4, 130.7, 131.5, 135.6.

MS (EI): *m*/*z* (%) = 171 ($M^+$, 94), 170 (100).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.65; N, 8.18. Found: C, 84.11; H, 7.71; N, 8.20.

## Acknowledgment

We thank MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca) for financial support (COFIN 2003). The authors are grateful to Centro Interdipartimentale Grandi Strumenti (CIGS) at the Università di Modena e Reggio Emilia for valuable assistance in NMR acquisition and mass spectrometric determinations, and to Prof. Franco Ghelfi (Dipartimento di Chimica, Università di Modena e Reggio Emilia) for providing chlorine delivery facilities at his laboratory. A.S. thanks Fondazione Cassa di Risparmio di Modena for a post-doctoral grant.

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