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Synthesis of *N*-Phenylpyrrole Carboximides

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Abstract: Several *N*-phenylpyrrole carboximides were synthesised using acyl isocyanates as intermediates.

Keywords: Acyl isocyanates, *N*-phenylpyrrole.

Introduction

During a certain stage of our synthetic approach towards potential protein tyrosine kinases inhibitors (see *e. g.* [1], [2]), compounds of the general structure **1** were required (Figure 1). Acyl isocyanates were used as intermediates for the synthesis of the imides of type **1**. One route to this type of compounds consisted in the addition of a C-nucleophile to the isocyanate of a pyrrolecarboxylic acid, whereas in a different approach, an acyl isocyanate was used as the electrophile in a Friedel-Crafts type substitution of a suitable pyrrole derivative.

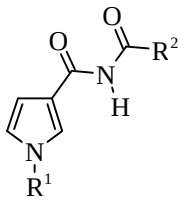
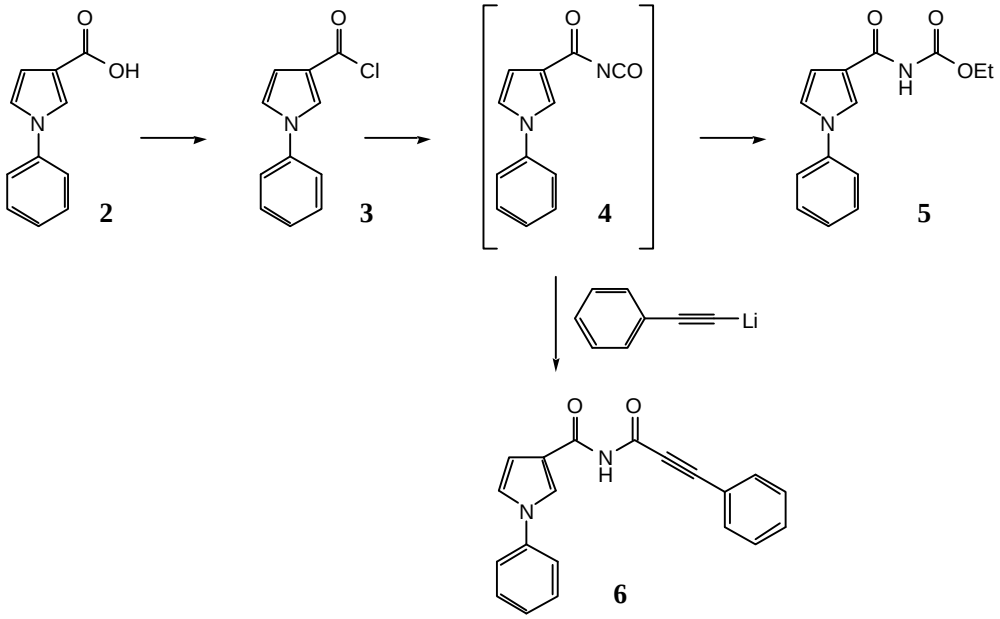


Figure 1. General structure of target compounds.

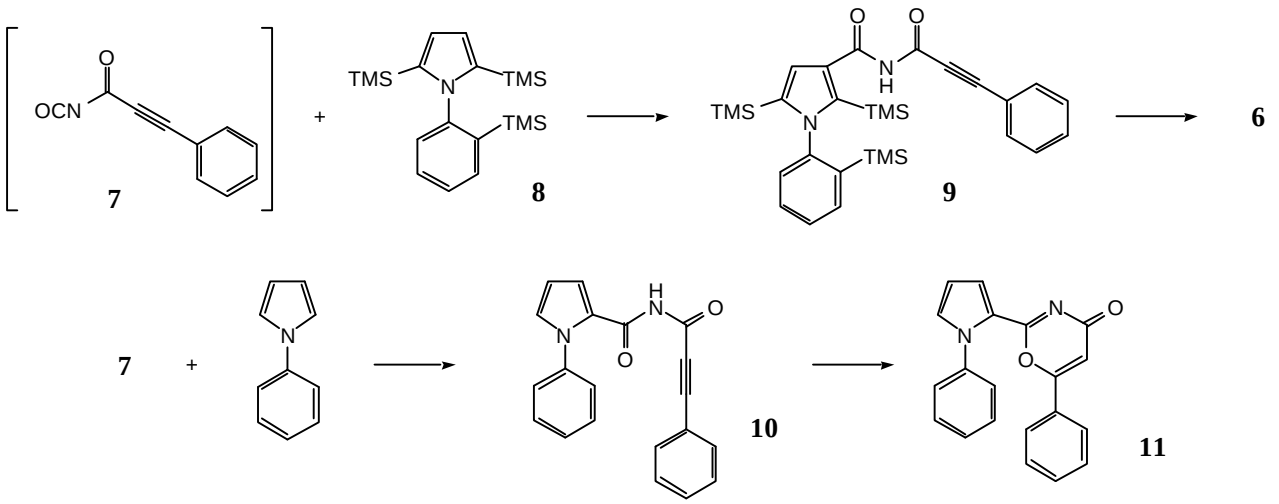
Results and Discussion

Reaction of *N*-phenylpyrrole-3-carboxylic acid (**2**) with thionyl chloride (Scheme 1) gave the acid chloride **3**, which was treated with tetrabutylammonium isocyanate in tetrahydrofuran to yield the corresponding acyl isocyanate **4**. This sensitive compound could not be isolated, but its formation was easily demonstrated by quenching the reaction with ethanol, whereupon the acylated carbamate **5** was obtained. Reaction of **4** with lithium phenylacetylide gave the imide **6**.



Scheme 1. Synthesis of imide **6**.

Using the second approach mentioned, the isocyanate **7**, which had been obtained from phenylpropiolamide and oxalyl chloride in dichloromethane, was reacted (Scheme 2) with the suitably protected *N*-phenylpyrrole **8**. Imide **9** was obtained in good yield; deprotection to **6**, however, was difficult and could be achieved in only 23%. When unprotected *N*-phenylpyrrole was treated with the isocyanate **7**, substitution took place predominantly in the 2-position of the pyrrole ring, yielding **10**. This latter compound cyclised to the oxazinone **11** upon heating. The structure of **11** was obtained from X-ray diffraction [3].



Scheme 2. Alternate synthesis of imide **6** and formation of oxazinone **11**.

Experimental

General

Chemicals were purchased from *Fluka AG*, *Aldrich Chemical Company, Inc.*, *Merck GmbH*, or *Lancaster Synthesis Ltd.* Solvents used in reactions were distilled and dried or purchased in *absolute* quality. Tetrahydrofuran was freshly distilled from Na/K. TLC: *Merck* silica gel 60 F_{254} precoated glass plates. Column chromatography: flash-chromatography procedure of *Still* et al. [4]; columns with water cooling; *Merck* Kieselgel 60, 40-63 μm.

M.p.: *Kofler* hot stage, corrected. IR: *Perkin-Elmer* FT-IR 1600; KBr pellet or liquid film between NaCl plates. NMR: *Varian Gemini 300* (^{1}H: 300 MHz, ^{13}C: 75 MHz); chemical shifts *d* in ppm relative to TMS (0 ppm); coupling constants *J* in Hz; multiplicities of ^{13}C resonances from APT and/or ^{1}H,^{13}C COSY experiments; * means that similar assignments may be interchanged within the same spectrum. MS: *VG 70-250* (Dr. *H. Nadig*); FAB MS: *VG ZAB HF* (courtesy *Ciba-Geigy AG*, Basel).

1-Phenyl-1*H*-pyrrole-3-carbonyl chloride (**3**)

A solution of 1-phenyl-1*H*-pyrrole-3-carboxylic acid [5] (**2**, 104 mg, 556 μmol) and thionyl chloride (700 μL, 9.62 mmol) in hexane (2 mL) was stirred under Ar for 5 h. The solvent was removed to give 126 mg of **3** as a brownish oil (containing 10-20% of the carboxylic acid), which was used without further purification [6].

Ethyl *N*-(1-phenyl-1*H*-pyrrole-3-carbonyl)carbamate (**5**)

Tetrabutylammonium isocyanate (279 mg, 981 μmol) was dried *in vacuo* at 65° for 1 h, disssolved

under Ar in tetrahydrofuran (1.7 mL), and the solution cooled to –78°. Ethanol (abs, 50 μL), and then a precooled solution of **3** (110 mg, 535 μmol) were added under Ar. The mixture was stirred for 3 h and then the solvent removed *in vacuo*. The residue was chromatographed on SiO_2 (27 g, dichloromethane/ethyl acetate 8:1) to give 26 mg (19%) of **5** as a colorless solid, 20 mg (20%) of 1-phenyl-1*H*-pyrrole-3-carboxamide, and 37 mg of unidentified by-products.

Colorless solid, m.p. 44-46°.

IR (KBr): 3279; 3132; 2980; 2930; 1750; 1676; 1599; 1511; 1269; 1201; 1057; 1033; 901; 758; 692.

^{1}H NMR (300 MHz, $CDCl_3$): 8.01 (s, 1H, NH); 7.78 (t, *J* = 2.0, 1H, H-C(2)); 7.5-7.3 (m, 5H, phenyl-H); 7.05 (dd, *J* = 2.3, 3.1, 1H, H-C(5)); 6.67 (dd, *J* = 3.0, 1.7, 1H, H-C(4)); 4.30 (q, *J* = 7.1, 2H, CH_2); 1.33 (t, *J* = 6.9, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): 161.1 (C=O); 151.4 (O-C=O); 139.5 (phenyl C(1)); 129.8 (phenyl C(3), C(5)); 127.2 (phenyl C(4)); 124.0 (C(2)); 121.1 (C(5)); 121.0 (phenyl C(2), C(6)); 120.2 (C(3)); 109.5 (C(4)); 62.1 (CH_2); 14.3 (CH_3).

EI MS: 259 (3); 258 (20, M^+); 212 (13); 171 (13); 170 (100, [*M*–NH-$COOC_2H_5$]$^+$); 115 (13); 77 (17); 51 (12).

Anal. Calcd for $C_{14}H_{14}N_2O_3$ (258.28): C, 65.11; H, 5.46; N, 10.85; O, 18.58. Found: C, 64.91; H, 5.67; N, 10.04; O, 17.11.

N-(3-Phenyl-2-propynoyl)-1-phenyl-1*H*-pyrrole-3-carboxamide (**6**) from 1-phenyl-1*H*-pyrrole-3-carbonyl chloride (**3**)

To a solution of tetrabutylammonium cyanate (909 mg, 3.20 mmol) in tetrahydrofuran (12 mL), 1-phenyl-1*H*-pyrrole-3-carbonyl chloride (**3**, 465 mg, 2.26 mmol) was added under Ar. After stirring the mixture for 90 min at 0°, lithium phenylacetylide (2.26 ml, 1.0 M in tetrahydrofuran, 2.26 mmol) was added and the mixture stirred for additional 3 h at 0°. The solvent was removed *in vacuo* and the residue chromatographed on SiO_2 (100 g, dichloromethane) to give 104 mg (15%) of **6** as a colorless solid.

Colorless needles (dichloromethane/pentane), m.p. 149-151°.

IR (KBr): 3251; 3151; 2230; 2196; 1709, 1637; 1336; 1250; 754; 747.

^{1}H NMR (300 MHz, $CDCl_3$): 9.79 (*s br*, 1H, NH); 8.03 (*t*, *J* = 2.0, 1H, H-C(2)); 7.67 (*dd*, *J* = 6.8, 1.5, 2H, H-C(2), C≡C-phenyl H-C(6)); 7.45-7.35 (*m*, 8H, phenyl-H); 7.10 (*t*, *J* = 3.1, 1H, H-C(5)); 6.89 (*dd*, *J* = 3.1, 1.8, 1H, H-C(4)).

^{13}C NMR (75 MHz, $CDCl_3$): 161.2, 153.8 (2 × C=O); 139.5 (*N*-phenyl C(1)); 133.1 (C≡C-phenyl C(2), C(6)); 130.7 (C≡C-phenyl C(4)); 129.8, 128.5 (*N*-phenyl C(3), C(5), and C≡C-phenyl C(3), C(5)); 127.1 (*N*-phenyl C(4)); 124.4 (C(2)*); 121.3 (C(5)*); 120.8 (*N*-phenyl C(2), C(6)); 120.1 (C≡C-phenyl C(1)*); 119.6 (C(3)*); 110.5 (C(4)); 93.5 (*C*≡C-CO); 83.3 (C≡*C*-CO).

EI MS (70 eV): 314 (7, M^+); 168 (100); 140 (5); 118 (24); 105 (10); 90 (7); 77 (15, [C_6H_5]$^+$); 51

(7).

CI MS (NH_3): 315 (100, [*M*+H]$^+$); 186 (11, [C_6H_5-C_4H_3N-$CONH_2$]$^+$); 164 (5).

EI HRMS (70 eV): Calcd for $C_{20}H_{14}N_2O_2$: 314.1055. Found: 314.1049.

2,5-Bis(trimethylsilyl)-1-[2-(trimethylsilyl)phenyl]-1*H*-pyrrole (**8**)

Butyllithium (100 mL, 1.6 M in hexane, 160.0 mmol) was added under Ar to 1-phenyl-1*H*-pyrrole (5.09 g, 36.0 mmol) and *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (22.5 mL, 160.0 mmol). The mixture was refluxed for 23 h and then cooled to –78°. Trimethylchlorosilane (20.0 mL, 160.0 mmol) was added and the mixture stirred for 6 h at 0° and for 90 min at room temperature. After washing twice with sat. NH_4Cl solution and then with water, the organic layer was dried (Na_2SO_4), filtered, and the solvent evaporated. The crude product (12.4 g of a yellowish oil) was purified in ten portions by chromatography on SiO_2 (150 g, pentane/dichloromethane 12:1) to give 4.85 g (37%) of **8** as a yellowish oil. An analytically pure sample was obtained by kugelrohr distillation (175°/0.13 mbar).

IR (NaCl): 3060; 2956; 2897; 1479; 1247; 1166; 1120; 931; 837; 757.

^{1}H NMR (300 MHz, $CDCl_3$): 7.54 (*dd*, *J* = 7.3, 1.8, 1H, phenyl H-C(3)); 7.38 (*td*, *J* = 7.4, 1.5, 1H, phenyl H-C(4)*); 7.31 (*td*, *J* = 7.4, 1.7, 1H, phenyl H-C(5)*); 7.15 (*dd*, *J* = 7.7, 1.2, 1H, phenyl H-C(6)); 6.48 (*s*, 2H, H-C(3), H-C(4)); –0.01 (*s*, 9H, $(CH_3)_3$Si-phenyl); –0.09 (*s*, 18H, $(CH_3)_3$Si-pyrrole).

^{13}C NMR (75 MHz, $CDCl_3$): 147.9 (*s*, phenyl C(1)); 140.2 (*s*, phenyl C(2)); 140.0 (*s*, C(2), C(5)); 135.2 (*d*, phenyl C(3); 130.0, 128.4, 127.8 (3*d*, phenyl C(4), C(5), C(6)); 119.1 (*d*, C(3), C(4)); 0.3 (*q*, $(CH_3)_3$Si-pyrrole); –0.5 (*q*, $(CH_3)_3$Si-phenyl).

EI MS (70 eV): 359 (10, *M*$^+$); 286 (24, [*M*–Si$(CH_3)_3$]$^+$); 256 (23); 240 (5); 212 (9); 198 (14); 73 (100, [Si$(CH_3)_3$]$^+$).

CI MS (NH_3): 360 (100, [*M*+H]$^+$); 288 (21, [*M*–Si$(CH_3)_3$+2H]$^+$); 214 (7); 90 (30); 73 (6, [Si$(CH_3)_3$]$^+$).

N-(3-Phenyl-2-propynoyl)-2,5-bis(trimethylsilyl)-1-[2-(trimethylsilyl)phenyl]-1*H*-pyrrole-3-carboxamide (**9**)

To a solution of 3-phenyl-2-propynamide [7] (741 mg, 5.10 mmol, prepared from 3-phenyl-2-propynoyl chloride [8]) in dichloromethane (12 mL), oxalyl chloride (482 µL, 5.62 mmol) was added under Ar at room temperature. The mixture was refluxed for 135 min and then cooled to 0°. 2,5-Bis(trimethylsilyl)-1-[2-(trimethylsilyl)phenyl]-1*H*-pyrrole (**8**, 820 µL, 2.10 mmol) in dichloromethane (5 mL) was added under Ar, followed by $AlCl_3$ (1.472 g, 11.04 mmol). The mixture was stirred for 22 h at 0° and then poured into ice/water (100 mL). After stirring for 2.5 h, the organic phase was separated, dried (Na_2SO_4), filtered, and the solvent evaporated *in vacuo*. The residue was chromatographed on SiO_2 (95g, gradient dichloromethane → dichloromethane/methanol 99:1) to give 852 mg (76%) of **9** as a colorless solid.

Colorless prisms (*tert*-butyl methyl ether/pentane), m.p. 175-177°.

IR (KBr): 3272; 3059; 2954; 2896; 2234; 2199; 1703; 1634; 1336; 1215; 838; 760.

^{1}H NMR (300 MHz, $CDCl_3$): 8.87 (*s br*, 1H, NH); 7.66 (*dt*, *J* = 6.7, 1.6, 2H, C≡C-phenyl H-C(2), H-C(6)); 7.57 (*dd*, *J* = 7.4, 1.5, 1H, *N*-phenyl H-C(3)); 7.47-7.33 (*m*, 5H, phenyl-H); 7.12 (*dd*, *J* = 7.6, 1.5, 1H, *N*-phenyl H-C(6)); 6.78 (*s*, 1H, H-C(4)); 0.02, –0.01, –0.07 (3*s*, 3 × 9H, 3 × $(CH_3)_3$Si).

^{13}C NMR (75 MHz, $CDCl_3$): 161.7*s*, 152.8*s* (2 × C=O); 147.0*s*; 146.9*s*; 141.5*s*; 139.9*s*; 135.4*d*; 133.2*d*; 130.6*d*; 129.7*d*; 128.8*d*; 128.6*d*; 128.5*d*; 126.3*s*; 120.4*s*; 118.8*d*; 91.8*s* (*C*≡C-CO); 83.2*s* (C≡*C*-CO); 0.1*q*, –0.1*q* –0.7*q* (3 × $(CH_3)_3$Si).

EI MS (70 eV): 530 (6, M^+); 515 (9, $[M–CH_3]^+$); 457 (7, $[M–Si(CH_3)_3]^+$); 384 (28, $[M–2×Si(CH_3)]^+$); 311 (23, $[M–3×Si(CH_3)_3]^+$); 129 (17); 118 (9); 89 (5); 77 (5, $[C_6H_5]^+$); 73 (100, $[Si(CH_3)_3]^+$); 45 (15).

Anal. Calcd for $C_{29}H_{38}N_2O_2Si_3$ (530.89): C, 65.61; H, 7.22; N, 5.28. Found: C, 65.72; H, 7.30; N, 5.10.

N-(3-Phenyl-2-propynoyl)-1-phenyl-1*H*-pyrrole-3-carboxamide (**6**) from (**9**)

N-(3-Phenyl-2-propynoyl)-2,5-bis(trimethylsilyl)-1-[2-(trimethylsilyl)phenyl]-1*H*-pyrrole-3-carboxamide (**9**, 87 mg, 164 μmol) and tetrabutylammonium fluoride trihydrate (218 mg, 691 μmol) were stirred in tetrahydrofuran for 50 min at 60°. The mixture was then taken up with dichloromethane and washed with water. The organic phase was separated, dried over Na_2SO_4, filtered, and the solvent removed *in vacu*o. The residue was chromatographed on SiO_2 (15 g, dichloromethane/methanol 99:1) to give 12 mg (23%) of **6** as a colorless solid.

N-(3-Phenyl-2-propynoyl)-1-phenyl-1*H*-pyrrole-2-carboxamide (**10**) and 1,2-bis-(1-phenyl-1*H*-pyrrol-2-yl)-ethane-1,2-dione (**12**)

To a solution of 3-phenyl-2-propynamide [7] (812 mg, 5.59 mmol) in dichloromethane (12 mL), oxalyl chloride (527 μL, 6.15 mmol) was added under Ar at room temperature. The mixture was refluxed for 150 min. 1-Phenyl-1*H*-pyrrole (820 mg, 5.73 mmol) in dichloromethane (3 mL) was added and the mixture refluxed for 45 h. The solvent was removed and the residue chromatographed on SiO_2 (100 g, gradient dichloromethane → dichloromethane/methanol 99:1 → dichloromethane/methanol 98:2) to give 813 mg (46%) of **10**.

Colorless needles (dichloromethane/pentane), mp. 125-127°.

IR (KBr): 3215; 3125; 2211; 1702; 1654; 1598; 1498; 1261; 1187; 1170; 754; 744; 694.

^{1}H NMR (300 MHz, $CDCl_3$): 8.74 (*s br*, 1H, NH); 7.55 (*dd*, *J* = 6.9, 1.5, 2H, C≡C-phenyl H-C(2), H-C(6)); 7.47-7.30 (*m*, 8H, phenyl-H); 7.06 (*dd*, *J* = 4.0, 1.7, 1H, H-C(3)); 7.04 (*dd*, *J* = 2.7, 1.7, 1H, H-C(5)); 6.35 (*dd*, *J* = 4.0, 2.7, 1H, H-C(4)).

^{13}C NMR (75 MHz, $CDCl_3$): 157.0*s*, 152.9*s* (2 × C=O); 139.8*s* (*N*-phenyl C(1)); 132.9*d* (C≡C-

phenyl C(2), C(6)); 131.4*d* (C(5)); 130.5*d* (C≡C-phenyl C(4)); 128.8*d* (C≡C-phenyl C(3), C(5)); 128.3*d* (*N*-phenyl C(3), C(5)); 127.8*d* (*N*-phenyl C(4)); 125.8*d* (*N*-phenyl C(2), C(6)); 124.4*s* (C(2)); 119.8*s* (C≡C-phenyl C(1)); 118.3*d* (C(3)); 109.7*d* (C(4)); 92.4*s* (*C*≡C-CO); 82.9*s* (C≡*C*-CO); assignments from ^{1}H,^{13}C COSY.

EI MS (70 eV): 314 (25, M^+); 291 (13); 168 (100); 140 (12); 118 (55); 105 (28); 90 (16); 77 (36, $[C_6H_5]^+$); 51 (22).

Anal. Calcd for $C_{20}H_{14}N_2O_2$ (314.34): C, 76.42; H, 4.49; N, 8.91; O, 10.18. Found: C, 76.33; H, 4.48; N, 8.85; O, 10.23.

As a by-product, 1,2-bis-(1-phenyl-1*H*-pyrrol-2-yl)-ethane-1,2-dione (**12**, 168 mg, 9%) was isolated.

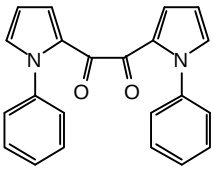


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Figure 2.

Yellow leaflets (dichloromethane/pentane), m.p. 127.5-130.5°.

IR (KBr): 3127, 3064; 1644; 1629; 1495; 1407; 1351; 777; 753; 733; 698.

^{1}H NMR (300 MHz, $CDCl_3$): 7.41-7.27 (*m*, 10H, phenyl-H); 7.10 (*dd*, *J* = 4.1, 1.7, 2H, pyrrole H-C(3)); 7.03 (*dd*, *J* = 2.5, 1.7, 2H, pyrrole H-C(5)); 6.28 (*dd*, *J* = 4.1, 2.5, 2H, pyrrole H-C(4)).

^{13}C NMR (75 MHz, $CDCl_3$): 181.2 (C=O); 139.8 (phenyl C(1)); 132.9 (pyrrole C(3)*); 128.6 (phenyl C(3'), C(5)); 128.2 (pyrrole C(2)); 127.8 (phenyl C(4')); 125.7 (phenyl C(2), C(6)); 124.9 (pyrrole C(5)*); 110.4 (pyrrole C(4')).

EI MS (70 eV): 340 (7, M^+); 170 (100, $[C_6H_5C_4H_3NCO]^+$); 115 (31); 77 (5, $C_6H_5]^+$).

Anal. Calcd for $C_{20}H_{16}N_2O_2$ (340.38): C, 77.63; H, 4.74; N, 8.23. Found: C, 77.15; H, 4.73; N, 8.19.

6-Phenyl-2-(1-phenyl-1*H*-pyrrol-2-yl)-[1,3]oxazin-4-one (**11**)

N-(3-phenyl-2-propynoyl)-1-phenyl-1*H*-pyrrole-2-carboxamide (**10**, 33 mg, 105 mmol) was heated under Ar to 160° for 25 min. After cooling, the brownish oil was chromatographed on SiO_2 (24 g, dichloromethane/methanol 99:1) to give 22 mg (67%) of **11** as a brownish solid.

Yellowish prisms (hexane/dichloromethane), m.p. 174-176°.

IR (KBr): 3075; 2922; 1671, 1640; 1553; 1495; 1448; 1348; 948; 767; 734; 698.

^{1}H NMR (300 MHz, $CDCl_3$): 7.56 (*dd*, *J* = 4.0, 1.8, 1H, pyrrole H-C(3)); 7.49-7.39 (*m*, 6H, *N*-phenyl-H and C=C-phenyl H-C(4)); 7.26 (*t*, *J* = 8, 2H, C=C-phenyl H-C(3), H-C(5)); 7.09 (*dd*, *J* = 2.6, 1.8, 1H, pyrrole H-C(5)); 6.94-6.90 (*m*, 2H, C=C-phenyl H-C(2), H-C(6)); 6.48 (*s*, 1H, H-C(5)); 6.45

(*dd*, *J* = 4.0, 2.6, 1H, pyrrole H-C(4)).

^{13}C NMR (75 MHz, $CDCl_3$): 168.1*s* (C(4)); 162.2*s*, 158.8*s* (C(2), C(6)); 140.7*s* (*N*-phenyl C(1)); 132.2*d* (pyrrole C(5)); 131.7*d* (C=C-phenyl C(4)); 129.2*s* (C=C-phenyl C(1)); 128.2*d* (*N*-phenyl C(4)); 129.5*d*, 128.8*d*, 126.0*d*, 125.3*d* (C=C-phenyl and *N*-phenyl C(3), C(5), C(2), C(6)); 123.1*s* (pyrrole C(2)); 122.3*d* (pyrrole C(3)); 111.0*d* (pyrrole C(4)); 103.8*d* (C(5)); assignments from ^{1}H,^{13}C COSY.

EI MS (70 eV): 314 (22, M^+); 168 (100); 140 (7); 115 (10); 77 (19, $[C_6H_5]^+$).

Anal. Calcd for $C_{20}H_{14}N_2O_2$ (314.34): C, 76.42; H, 4.49; N, 8.91; O, 10.18. Found: C, 76.42; H, 4.62; N, 8.64; O, 10.22.

Crystals obtained from ethanol/water were subjected to X-ray structure determination [3].

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Sample Availability: Available from the authors.