10.1071/CH07132_ AC

Accessory Publication: Australian Journal of Chemistry, 2007, 60(8), 624–626.

Accessory Information

Synthesis of 5-phenyl 2-Functionalized Pyrroles by amino Heck and tandem amino Heck Carbonylation reactions

Shazia Zaman,[*A,B] Mitsuru Kitamura[B, C] and Andrew D. Abell[A]

[*A] *Department of Chemistry, University of Canterbury, Private bag 4800, Christchurch New Zealand*

[B]*Department of Chemistry, Graduate School of Science, 7-3-1 Hongo, Bunkyo-Ku Tokyo 113-0033, Japan*

[C] *Department of Applied Chemistry, Kyushu Institute of Technology, 1-1 Sensui-cho, Tobata-ku, Kitakyushu 804-8550, Japan*

shazia.zaman@canterbury.ac.nz

General Experimental Procedures

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on 500 and 300 MHz spectrometers in $CDCl_3$ using tetramethylsilane (for ^{1}H: δ = 0) and $CDCl_3$ (for ^{13}C: δ = 77.0) as internal standard. High-resolution mass spectra were obtained with a JEOL JMS-700P mass spectrometer. Elemental analyses were carried out at The Elemental Analysis Laboratory, Department of Chemistry, Faculty of Science, the University of Tokyo. Flash column chromatography was performed on silica gel (Merck Silica gel 60, and Kanto Chemical Co., Inc. Silica gel 60N (spherical, neutral). *N*, *N*-Dimethylformamide (DMF) was distilled under reduced pressure calcium hydride, and stored over Molecular Sieves 4A under an argon atmosphere. Dichloromethane was distilled from calcium hydride, and stored over Molecular Sieves 4A. Triethylamine was distilled from CaH_2, and stored over Molecular sieves.

$Pd(PPh_3)_4$ was prepared by the literature procedure.[1] Pentafluorobenzoyl chloride was purchased from Tokyo Chemical Industry Co., Ltd. and used without purification. Dehydrated THF and diethyl ether were purchased from Kanto Chemical CO., Inc.

1-Phenylpent-4-yn-1-one **(2)**

Acetophenone *N*,*N*-dimethyl hydrazone[2] **1** (2.0 g, 12.32 mmol) was treated with freshly prepared LDA [from *n*-BuLi (1.6 M in hexane, 7.7 mL) and *N*,*N*-diisopropylamine (2.6 mL) in THF (25 mL)] at 0 ºC and stirred for 1 h under argon atmosphere. 4-Bromo-1-butyne (0.92 mL) in THF (4 mL) was added to it. The reaction was stirred continuously, warmed to rt overnight and quenched by adding aqueous sat. NH_4Cl solution. The reaction mixture was then extracted with ether (×3). The combined organic fractions were washed with water, brine, dried over anhydrous $MgSO_4$ and evaporated in vacuo to give crude the alkylated hydrazone which was used in the next step without further purification.

The crude alkylated hydrazone was then hydrolyzed by adding acetic acid (5.9 mL, 104 mmol), sodium acetate (2.83 g, 20.85 mmol), water (0.7 mL), and THF (3.3 mL) were added and the mixture was stirred at rt for five hours. The reaction was quenched by adding aqueous NaOH solution at 0 °C and the mixture was extracted with ether (×3). The combined organic extracts were washed with water, brine, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude product was then purified by flash column chromatography (H/EA = 93/7) to give 1.1 g (91%) of ***2*** as a yellow oil.

(Found: C 83.32, H 6.49%. $C_{13}H_{10}O$ requires C 83.51, H 6.37%); ^{1}H NMR (500 MHz) δ 1.99 (1H, t, *J* 2.5, 5-C*H*), 2.63 (2H, dt, *J* 8, 3, 3-CH_2), 3.24 (2H, t, *J* 7.5, 2-CH_2), 7.45 (2H, t, *J* 8, *Ar*), 7.57-7.59 (1H, m, *Ar*), 7.96 (2H, d, *J* 8, ***Ar***); ^{13}C NMR (75

MHz) δ 13.1 (*C*H_2, C-3), 37.4 (*C*H_2, C-2), 68.7 (*C*H, C-5), 83.3 (*C*≡CH, C-4), 127.9, 128.6, 133.2, 136.4 (*Ar*), 197.5 (*C*-1).

2-But-3-yn-1-yl-2-phenyl-1,3-dioxolane **(3)**

A solution of the ketone **2** (1.90 g, 12.04 mmol) in benzene, ethylene glycol (2.5 mL, 45.17 mmol) and a catalytic amount of *p*-TsOH were refluxed for 3 h using a Dean-Stark apparatus for removal of water. The reaction was quenched by adding sat. $NaHCO_3$ soln (aq.), extracted with ethyl acetate (×3), washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by recrystallization from n-hexane to give 2.3 g (95%) of ***3*** as a colorless solid.

(Found: C 76.91, H 7.05%. $C_{13}H_{14}O_2$ requires C 77.20, H 6.97%); ^{1}H NMR (500 MHz) δ 1.89 (1H, t, *J* = 2.5, 4-C*H*), 2.14-2.17 (2H, m, 1-CH_2), 2.27-2.30 (2H, m, 2-CH_2), 3.77 (2H, t, *J* 7, 4'-CH_2O), 4.01 (2H, t, *J* 7, 5'-CH_2O), 7.28-7.31 (1H, m, *Ar*), 7.34 (2H, t, *J* 7.5, *Ar*), 7.43-7.45 (2H, m, *Ar*); ^{13}C NMR (75 MHz) δ 13.1 (*C*-2), 39.3 (*C*-1), 64.6 (*C*-4', 5'), 67.8 (*C*-4), 84.1 (*C*-3), 109.3 (*C*-2'), 125.9, 128.01, 128.2, 141.9 (*Ar*).

Methyl 5-(2-phenyl-1,3-dioxolan-2-yl)pent-2-ynoate **(4)**

n-Butyl lithium (1.6 M in hexane, 2.2 mL) was added to a solution of **3** (684 mg, 3.38 mmol) in THF (15 mL) at -78 ºC and stirred for 1 h at the same temperature. Methyl chloroformate (0.05 mL, 4.06 mmol) in THF (5 mL) was added to the reaction mixture and stirred for 1 h. The reaction was quenched by adding NH_4Cl (sat.), extracted with ether (×3), washed with H_2O (×2), brine (×2), dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash column chromatography (H/EA = 90/10) to give 780 mg (88%) of ***4*** as a cream solid.

^{1}H NMR δ 2.18 (2H, t, *J* 7.5, 5-C*H*$_2$), 2.43 (2H, t, *J* 7.7, 4-C*H*$_2$), 3.73 (3H, s, C*H*$_3$), 3.78 (2H, ddd, *J* 7.3, 6.0, 3.4, 4'-C*H*$_2$), 4.01 (2H, ddd, *J* 7.4, 6.1, 3.6, 5'-C*H*$_2$), 7.28-7.36 (3H, m, *Ar*), 7.42-7.44 (2H, m, *Ar*); ^{13}C NMR δ 13.4 (*C*-4), 38.1 (*C*-5), 52.5 (*C*H$_3$), 64.7 (*C*-4',5'), 72.6 (*C*-2) 89.4 (*C*-3), 109.0 (*C*-2'), 125.7, 128.2, 128.3, 141.6 (*Ar*), 154.2 (*C*-1).

Methyl 6-oxo-6-phenylhex-2-ynoate **(5)**

A solution of **4** (730 mg, 2.80 mmol) in THF (15 mL) and 1 N HCl (aq. 10 mL) was stirred at 40 ºC for 4.5 h. NaHCO$_3$ soln. (sat) was added to the mixture, extracted with ether (×3), washed with H$_2$O (×2), brine (×1), dried (MgSO$_4$) and evaporated in vacuo. The crude product was purified by column chromatography (H/EA 90/10) to give 513 mg (84%) of ***5*** as a white solid.

(Found: C 72.13, H 5.61%. C$_{13}$H$_{12}$O$_3$ requires C 72.20, H 5.59%.); ^{1}H NMR (500 MHz) δ 2.79 (2H, t, *J* 7.5, 4-C*H*$_2$), 3.31 (2H, t, *J* 7.5, 5-C*H*$_2$), 3.76 (3H, s, C*H*$_3$), 7.49 (2H, t, *J* 7.5, *Ar*), 7.59 (1H, t, *J* 7.4, *Ar*), 7.96 (2H, d, *J* 7.4 Hz, *Ar*); ^{13}C NMR (75 MHz) δ 13.3 (*C*-4), 36.5 (*C*-5), 52.6 (*C*H$_3$), 73.1 (*C*-2), 88.3 (*C*-3), 128.0, 128.7, 133.5, 136.1 (*Ar*), 154.0 (*C*-1), 196.7 (*C*-6).

(EZ)-1-Phenylpent-4-yn-1-one oxime **(6a)**

The acetylenic ketone **5** (1.09 g, 6.90 mmol), hydroxylamine hydrochloride (1.19 g, 13.8 mmol) and pyridine (1.56 mL, 19.32 mmol) were stirred in ethanol (30 mL) at rt for 2 h. The reaction mixture was quenched by adding H$_2$O, brine and then 2 M HCl (aq.) and extracted with ethyl acetate (×3). The combined organic fractions were washed successively with 2 M HCl, sat. NaHCO$_3$ (aq), brine and dried over anhydrous Na$_2$SO$_4$, and concentrated in vacuo to give a (*E*/*Z*) mixture (5:2, based on

analysis of ^{1}H NMR spectrum) of crude oxime, which was purified by column chromatography using (H/EA = 92/8) to elute 997 mg (83%) of ***E-6a*** as a white solid first, and then 147 mg (12%) of ***Z-6a*** as a yellow solid, thus yielding the oxime in a combined yield of 95%.

Data for ***(E)-6a***

(Found: C 76.26, H 6.39, N 7.98%. $C_{11}H_{11}NO$: requires C 76.27, H 6.4, N 8.08%.); ^{1}H NMR (500 MHz) δ 1.98 (1H, t, *J* 3.0, 5-C*H*), 2.53 (2H, dt, *J* 7.5, 2.5, 3-CH_2), 3.06 (2H, t, *J* 7.5, 2-CH_2), 7.39-7.40 (3H, m, *Ar*), 7.63-7.64 (2H, m, *Ar*); ^{13}C NMR (75 MHz) δ 15.4 (*C*-3), 25.8 (*C*-2), 69.1 (*C*-5), 83.1 (*C-4*), 126.4, 128.6, 129.4, 135.1 (*Ar*), 157.9 (*C*-1).

Data for ***(Z)-6a***

^{1}H NMR (300 MHz) δ 1.98 (1H, t, *J* = 3.0 Hz, 5-C*H*), 2.37 (2H, dt, *J* 7.5, 3, 3-CH_2), 2.78 (2H, t, *J* 7.5, 2-CH_2), 7.37-7.70 (5H, m, *Ar*), 8.06 (1H, bs, O*H*); ^{13}C NMR (75 MHz) δ 16.0 (*C*-3), 34.4 (*C*-2), 69.4 (*C-5*), 82.7 (*C*-4), 127.7, 128.3, 129.1, 132.6 (*Ar*), 156.7 (*C*-1).

(E)-Methyl-6-(hydroxyimino)-6-phenylhex-2-ynoate **(6b)**

The aryl alkynyl ketone **5** (590 mg, 2.73 mmol), hydroxylamine hydrochloride (402 mg, 6.8 mmol) and pyridine (610 μL, 7.6 mmol) were stirred in EtOH (30 mL) at rt for 5 h. The reaction mixture was quenched by adding H_2O, brine and then 2 M HCl (aq.) and extracted with ethyl acetate(×3). The combined organic fractions were washed successively with 2 M HCl, sat. $NaHCO_3$ (aq), brine and dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the title compound as a single isomer, (based on analysis of ^{1}H NMR spectrum), which was purified by column

chromatography using (H/EA = 90/10) to elute 441 mg (70%) of *E*-***6b*** as a white solid.

^{1}H NMR (300 MHz) δ 2.66 (2H, t, *J* 7.9, 4-C*H*$_2$), 3.09 (2H, t, *J* 7.9, 5-C*H*$_2$), 3.75 (3H, s, C*H*$_3$), 7.36-7.43 (2H, m, *Ar*), 7.58-7.65 (2H, m, *Ar*), 8.10 (1H, bs, O*H*).

(*E*)-*1-Phenylpent-4-yn-1-one O-pentafluorobenzoyl oxime* (7a)

To a solution of *E*-**6a** (640 mg, 3.69 mmol) and TEA (1.0 mL, 7.38 mmol) in DCM (20 mL) at 0 ºC was added C_6F_5COCl (1.36 mg, 5.91 mmol) in DCM (5 mL) and stirred for 1.5 h. The reaction was quenched by adding H_2O at 0 ºC and extracted with ether (×3). The combined organic extracts were washed with water, brine, dried over anhydrous $MgSO_4$ and evaporated in vacuo. The crude oxime was purified by silica chromatography (H/EA = 95/5) to give 1.16 g (88%) of *E*-**7a** as a white solid.

Data for *E*-**7a**.

^{1}H NMR (500 MHz) δ 1.99 (1H, t, *J* 2.5, 5-C*H*), 2.50 (2H, dt, *J* 7.5, 2.5, 3-C*H*$_2$), 3.15 (2H, t, *J* 7.5, 2-C*H*$_2$), 7.40 (2H, t, *J* 7.5, *Ar*), 7.49-7.52 (1H, m, *Ar*), 7.77 (2H, d, *J* 8, *Ar*); ^{13}C NMR (75 MHz) δ 15.9 (*C*-2), 27.6 (*C*-3), 69.9 (*C*-5), 81.4 (*C-4*), 107.0 (m, *C*-F), 127.4, 128.7, 131.2, 132.5 (*Ar*), 135.8-139.6 (m, *C*-F), 141.6-145.4, 143.6-147.4, (m, *C*-F), 156.2 (O*C*O), 166.6 (*C*-1); TOF MS ES$^+$ [MH]$^+$: Found: 368.0637; Calcd for $C_{18}H_{11}F_5NO_2$: 368.0710.

***(E)-Methyl-6-(pentafluorobenzoyloxyimino)-6-phenylhex-2-ynoate* (7b)**

To a solution of *E*-**6b** (292 mg, 1.26 mmol) and TEA (350 μL, 2.53 mmol) in DCM (20 mL) at 0 ºC was added C_6F_5COCl (554 mg, 2.40 mmol) in DCM (5 mL) and stirred for 1.5 h. The reaction was quenched by adding H_2O at 0 ºC and extracted with ether (×3). The combined organic extracts were washed with water, brine, dried over

anhydrous $MgSO_4$ and evaporated in vacuo. The crude oxime was purified by recrystallization (H/EA) to give 420 mg (75%) of *E-**7b*** as a white solid. (Found: C 56.41; H 3.02; N 3.33%. $C_{20}H_{12}NO_4F_5$ requires C 56.48; H 2.84; N 3.29%.)

^{1}H NMR (500 MHz) δ 2.64 (2H, t, *J* 7.5, 4-C*H*$_2$), 3.21 (2H, t, *J* 7.5, 5-C*H*$_2$), 3.72 (3H, s, C*H*$_3$), 7.46 (2H, t, *J* 7.5, *Ar*), 7.51 (1H, t, *J* 7.0, *Ar*), 7.76 (2H, d, *J* 7.5, *Ar*); ^{13}C NMR (75 MHz) δ 16.14(*C*-4), 26.50 (*C*-5), 52.53 (*C*H$_3$), 73.86 (*C*-2), 85.97 (*C*-3), 127.4, 128.9, 131.4, 132.1 (*Ar*), 135.8-136.3, 139.2-139.7, 141.7-142-2, 143.6-143.9, 145.0-145.6, 147.0-147.6 (m, *C*-F), 153.6 (*C*-1), 156.0 (O*C*O), 196.7 (*C*-6).

References:

1. Coulson, D. R. *Inorg. Synth*. **1990**, *28*, 107.
2. Corey, E. J.; Enders, D. *Tetrahedron. Lett*. **1976**, 3. b) Corey, E. J.; Pearcepp, H. L. *J. Am. Chem. Soc*. **1979**, *101*, 5841. c) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res*. **2000**, *33*, 157.