JOC*Note*

Convergent Synthesis of the Quinolone Substructure of BILN 2061 via Carbonylative Sonogashira Coupling/Cyclization

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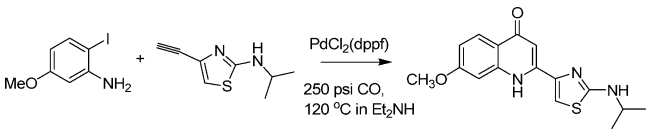

A convergent synthesis of quinolone **2** (key substructure of the protease inhibitor **BILN 2061**) was developed via palladium-catalyzed carbonylation of 2-iodo-5-methoxyaniline (**4**) with thiazolylacetylene **5**.

BILN 2061 has recently been reported as the first Hepatitis C virus (HCV) NS3 protease inhibitor that shows antiviral effects in infected humans.[1] A discovery synthesis of the drug was recently reported.[2] The thiazole moiety of the quinoline substructure was constructed through several transformations including an Arndt−Eistert reaction, which employs the unsafe reagent diazomethane (Scheme 1). As part of our studies on a scalable synthesis of **BILN 2061**, we became interested in devising a convergent approach to the quinolone subunit **2**. A preliminary scalable synthesis of **2** has recently been developed in our group, and it is based on the cyclization of aryl amide **3** (Scheme 1).[3]

In this Note we describe an alternative convergent synthesis of **2** based on the palladium-catalyzed carbonylative Sonogashira coupling[4] of 2-iodo-5-methoxyaniline (**4**) with thiazolylacetylene **5** (Scheme 1). This approach may also provide a practical and general access[4] to polysubstituted quinolones related to structure **2**.

The synthesis of **4** from the commercially available 4-iodo-3-nitroanisole is straightforward.[5] Reduction of 4-iodo-3-nitroanisole with hydrazine hydrate leads to **4** in 79% isolated yield [5a] (Scheme 2). A 93% yield has recently been reported in the reduction of 4-iodo-3-nitroanisole with hydrazine monohydrate in the presence of $FeCl_3$.[5b]

The synthesis of thiazolylacetylene **5** was accomplished by two different methods; the first one (Scheme 3) is based on the preparation of iodothiazole **8** from 2-isopropylaminothiazoline-4-one **6**.[6] Following Wiemer's protocol[7] for the synthesis of vinyl iodides from ketones, thiazolyl phosphate **7** was prepared from **6** in 83% yield, then it was converted without further purification to the desired iodothiazole **8** upon treatment with in situ generated TMSI. Sonogashira coupling[8] with TMS-acetylene provided the desired product **9** in quantitative yield. Removal of the TMS protecting group[9] was achieved in 98% isolated yield upon treatment of **9** with K_2CO_3/MeOH, providing the target substructure **5** ready for coupling with **4**.

An alternative synthesis of **5** introduces the acetylene upon coupling of lithiated TMS-acetylene to the previously reported[10] *N*-methoxy-*N*-methylchloroacetamide **10** to provide **11**[11] in 93% yield. Subsequently, **11** was converted, without further purification, to thiazole **9** upon treatment with isopropyl thiourea in 54% isolated yield over two steps. Cleavage of the TMS protecting group (K_2CO_3/MeOH) provided **5** in almost quantitative yield (Scheme 4).

Palladium-catalyzed carbonylative Sonogashira/cyclization of iodoanilines and iodophenols with terminal acetylenes has been reported to provide selective formation of quinolones and chromones, respectively, in high yields. On the basis of findings by Torii and Kalinin,[4] we expected that Et_2NH (used as solvent) should provide a good balance of basicity and steric hindrance for carbonylative coupling/cyclization of iodoanisidine **4** with thiazolylacetylene **5**. We hoped to be able to minimize formation of the corresponding amide **12** (Scheme 5) and promote formation of a six- vs five-membered ring (sometimes observed

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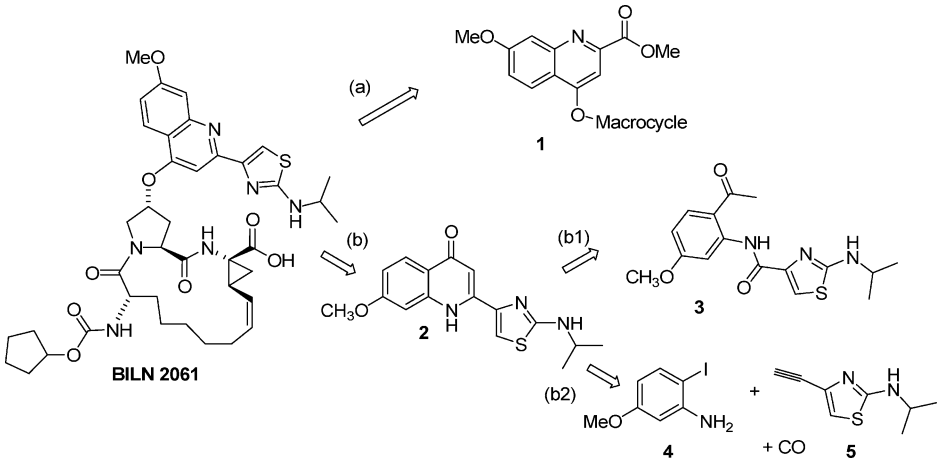
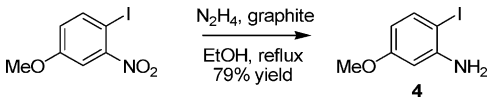
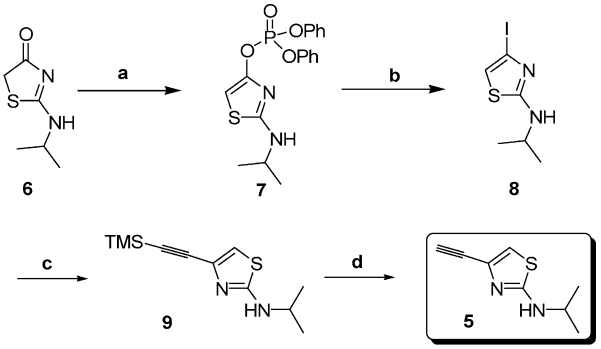
SCHEME 1. (a) Reported Discovery Approach and (b1, b2) Convergent Approaches



SCHEME 2

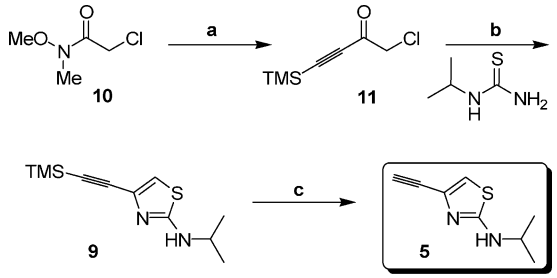


SCHEME 3



a: THF, KHMDS, -20 - 0°C, $(PhO)_2POCl$, 1.5 h, 83% yield;
b: NaI, TMSCl, CH_3CN, rt, 1h, 55% yield;
c: TMS-Acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 98%;
d: MeOH, K_2CO_3, 0 °C, 98%;

SCHEME 4. Alternative Synthesis of 5



a: TMS—≡—Li, Toluene, -20 - 0 °C;
b: THF, rt, 16h, 54% yield for two steps;
c: MeOH, K_2CO_3, 0 °C, 97%;

in related protocols[4,12]) by selective 6-*endo*-cyclization, by routing reactive intermediate **13** through intermediate **14**, and therefore direct the ring-closure to provide, regioselectively, the desired quinolone **2**.

Several reaction conditions for the coupling/cyclization sequence were examined and the key results are summarized in Table 1. The typical conditions (entry 1) provided the desired quinolone **2** in 71% assay yield with 3.8% of amide **12** and no detectable amount of **15**. The structure of **2** was confirmed by comparison of its ^1H NMR, ^{13}C NMR, and LCMS data to an authentic sample that was prepared by cyclization of amide **3** (Scheme 1, b1)[3].

A slightly improved yield was consistently obtained when $PdCl_2$(dppf) was used as catalyst. High conversion with low yield of quinolone **2** was obtained when $Pd(OAc)_2$ was used as catalyst (entry 3); in fact amide **12** was obtained as the major product under these conditions. Recent interest in the application of palladium−thiourea−dppp complex in carbonylative Sonogashira under mild conditions and its application in the synthesis of flavones[12] led us to examine these catalytic conditions for the formation quinolone **2** (entry 4). The results after 24 h at 50 °C indicate 50% conversion with less than 20% yield along with the formation of 10% of amide **12**. The reaction with $PdCl_2$-(dppf) was also run at lower temperature and CO pressure (entry 5): interestingly, complete conversion was detected after 24 h providing quinolone **2** in 60% yield, although higher levels of amide **12** were detected.

On the basis of the above data, we used $PdCl_2$(dppf) as catalyst in Et_2NH at 120 °C under 250 psi of CO, and obtained the desired quinolone **2** in 70% isolated yield. Amide **12** was detected in 2.9% as the major side-product in the reaction mixture, with no detectable amount of **15**. LCMS data indicated the presence of intermediates **13** and **14** at levels below 0.5%.

In summary, a convergent synthesis of **2**, the quinolone substructure of **BILN 2061**, was developed by applying Pd-catalyzed carbonylative annulation as the key step in the sequence. The synthesis of thiazoleacetylene **5** and the carbonylative Sonogashira/cyclization step may provide general access to structurally related quinolones.

Experimental Section

2-Iodo-5-methoxyaniline (4). A two-necked 100-mL flask, equipped with condenser, was charged with 4-iodo-3-nitroanisole (2.79 g, 10.0 mmol), graphite (3 g), and absolute ethanol (30 mL) under N_2 atmosphere. Hydrazine monohydrate (0.97 mL, 20.0 mmol) was added at 25 °C then the mixture was heated to reflux for 8 h. The reaction mixture was cooled to room temperature and filtered through Celite. The solvent was removed under reduced pressure and the product was purified by flash chromatography (40 g silica, EtOAc:Hex gradient from 1:8 to 1:1, respectively) to

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SCHEME 5. Formation of Quinolone 2

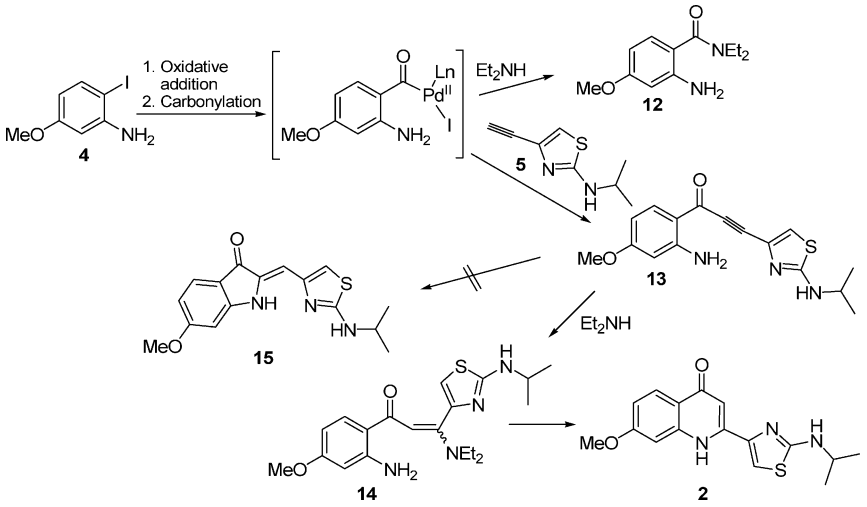

TABLE 1. Catalysts Effect on the Carbonylative Sonogashira Coupling/Cyclization

entry	catalyst	time, h	conditions	amide **12**,[a] %	yield,[b] %
1	$PdCl_2(PPh_3)_2$	6	250 psi CO, 120 °C in Et_2NH	3.8	71
2	$PdCl_2$(dppf)	6	250 psi CO, 120 °C in Et_2NH	2.9	73[c]
3	$Pd(OAc)_2$	6	250 psi CO, 120 °C in Et_2NH	68.3	25
4	$PdCl_2(PPh_3)_2$, thiourea-dppp,	24	50 psi CO, 50 °C, DBU in Et_2NH	10.4	<20
5	$PdCl_2$(dppf)	24	50 psi CO, 50 °C in Et_2NH	5.3	60

[a] Area % at 256 nm relative to quinolone **2**. [b] Yield was determined by HPLC quantitative assay. [c] 70% Isolated yield after column chromatography.

provide 1.97 g of the desired product in 79% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.7 Hz, 1H), 6.29 (d, J = 2.8 Hz, 1H), 6.11 (dd, J = 2.8, 8.7 Hz, 1H), 4.02 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 147.7, 138.9, 106.6, 100.0, 73.5, 55.1; NMR data are in full agreement with the published data for this compound in ref 5b.

4-Iodo-2-isopropylaminothiazoline (8). In a three-necked 500-mL flask, equipped with mechanical stirrer, N_2 inlet, and addition funnel, KHMDS (0.5 M in toluene, 96 mL, 48.0 mmol) was added to a cold (−20 °C) mixture of 2-isopropylaminothiazoline-4-one (5.09 g, 32.2 mmol) in dry THF (200 mL). The mixture was stirred for 20 min then diphenylchlorophosphate (10.0 mL, 48.3 mmol) was added at this temperature followed by stirring at 0 °C for an additional 90 min. The reaction mixture was then treated with 1.8 M NH_4OH (70 mL), and the product was extracted with MTBE (200 mL), dried over Na_2SO_4, then concentrated under reduced pressure to provide 10.43 g of the labile intermediate 2-isopropylaminothiazoline-4-diphenyl phosphate (**7**) in 83% yield. The product was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 5H), 7.26 (m, 5H), 5.97 (s, 1H), 5.07 (br s, 1H), 3.61 (m, 1H), 1.24 (d, J = 6.4, 6H).

NaI (8.94 g, 60 mmol) was added to the solution of crude phosphate **7** (7.7 g, 19.9 mmol) in dry acetonitrile (70 mL). The mixture was cooled to 0 °C followed by dropwise addition of TMS chloride (7.57 mL, 60 mmol). The reaction mixture was stirred at room temperature for 90 min, then quenched by addition of a saturated solution of $NaHCO_3$ (30 mL). CH_2Cl_2 (70 mL) was added, and the aqueous fraction was separated and extracted with CH_2Cl_2 (70 mL). The combined organics were dried over Na_2SO_4, then concentrated under reduced pressure. The product was purified by column chromatography (hexanes:EtOAc, 2:1, R_f 0.6) to give 3.5 g of **8** in 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 5.24 (br s, 1H), 3.63 (m, 1H), 1.29 (d, J = 6.4, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 109.8, 90.0, 49.1, 22.7; HRMS (APCI) calcd for $[M + H]^+$ $C_6H_{10}IN_2S$ 268.9609, found 268.9615.

ThiazoleTMS-acetylene (9): (a) From 4-iodo-2-isopropylaminothiazoline (8): To a solution of **8** (75.0 mg, 0.28 mmol) and TMS-acetylene (0.12 mL, 0.84 mmol) in Et_3N (3 mL) were added $PdCl_2(PPh_3)_2$ (19.7 mg, 0.028 mmol) and CuI (5.4 mg, 0.028 mmol) then the mixture was stirred under Ar atmosphere at reflux for 2 h. The reaction mixture was cooled to room temperature, diluted with MTBE (10 mL), then washed with brine. The organic fraction was concentrated under reduced pressure then the product was purified by column chromatography (Hex:EtOAc 4:1) to give 65.3 mg of the desired product **9** in 98% yield.

(b) From *N*-methoxy-*N*-methylchloroacetamide (10): To a cold (−20 °C) solution of TMS-acetylene in toluene (5 mL) was added LHMDS (8.0 mL, 1 M in THF, 8 mmol) dropwise over 2 min keeping $T < -5$ °C. The mixture was stirred at 0 °C for 30 min, then transferred to the cold (−10 °C) reaction mixture that contains amide **10** (1.0 g, 7.2 mmol) in toluene (10 mL) at a rate that kept $T < -5$ °C. The resulting mixture was stirred for 20 min at −5 °C then 1.5 h at room temperature, quenched by slow addition to cold 1 N HCl (5 mL) under N_2, then stirred for 5 min. The organic fraction was separated and washed with brine, then dried over Na_2SO_4. Evaporation of the solvents under reduced pressure provided crude **11** (1.17 g, 93% yield) which was used for next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (s, 2H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 103.1, 99.1, 49.4, −1.0; NMR data are in full agreement with the published data in ref 11.

A solution of crude α-chloroketone **11** (1.17 g, 6.7 mmol) and isopropylthiourea (0.792 g, 6.7 mmol) in THF (14 mL) was stirred at room temperature for 16 h. Water (10 mL) and MTBE (20 mL) were added, the organic fraction was separated, and the aqueous was washed with 2 × 6 mL of TBME. The combined organics were washed with brine, dried over Na_2SO_4, concentrated, and purified by flash chromatography (Hex:EtOAc 10:1, respectively) to give 0.86 g of pure product **9** in 54% isolated yield over the two steps. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.18 (br d, 1H), 3.39 (m, 1H), 1.05 (d, J = 6.5, 6H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 133.3, 111.9, 99.8, 93.5, 48.6, 22.9, 0.00; HRMS (APCI) Calcd for $[M + H]^+$ $C_{11}H_{19}N_2SSi$ 239.1038, found 239.1045.

4-Ethynyl-2-isopropylaminothiazoline (5). Alkyne **9** (1.0 g, 4.2 mmol) was dissolved in MeOH (30 mL), then cooled to 0 °C. K_2CO_3 (0.62 g, 4.5 mmol) was added and stirring was continued at 0

°C for an additional 1.5 h. The reaction was diluted with EtOAc (20 mL) and water (20 mL) and the aqueous fraction was washed with EtOAc, then the organics were combined, washed with brine, dried, and concentrated under reduced pressure to give 0.68 g of the desired product in >97% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70 (s, 1H), 5.5 (br s, 1H), 3.82 (m, 1H), 3.05 (s, 1H), 1.25 (d, J = 6.4, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 132.2, 112.2, 78.7, 76.1, 48.0, 22.8; HRMS (APCI) calcd for $[M + H]^+$ $C_8H_{11}N_2S$ 167.0643, found 167.0641.

2-(2-Isopropylaminothiazol-4-yl)-7-methoxy-4a,8a-dihydro-1*H*-quinolin-4-one (2). 2-Iodo-5-methoxyaniline (224.15 mg, 0.9 mmol) and thiazoleacetylene **5** (200.00 mg, 1.2 mmol) were stirred in Et_2NH (3 mL) in the presence of $PdCl_2$(dppf) (10.0 mg, 0.014 mmol) at 120 °C under 250 psi of CO for 6 h. The reaction was cooled to room temperature, then diluted with MeOH (20 mL). Water (40 mL) was added dropwise at room temperature in 20 min to precipitate the product, which after filtration and drying provided 1.2 g of crude product of 73% purity. Recrystallization from MeOH/water provided 0.88 g of pure product in 70% isolated yield. Mp 245−247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.95 (d, J = 8.9 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.50 (s, 1H), 7.28 (d, J = 2.3 Hz, 1H), 6.89 (dd, J = 2.3, 8.9 Hz, 1H), 6.52 (d, J = 1.6 Hz, 1H), 3.98 (m, 1H), 3.87 (s, 3H), 1.22 (d, J = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 176.6, 167.6, 161.9, 144.0, 143.4, 141.8, 126.4, 119.5, 113.0, 106.6, 105.6, 99.6, 55.4, 46.2, 22.3; HRMS (APCI) calcd for $C_{16}H_{18}N_3O_2S$ 316.1114, found 316.1108. Analytical data are in full agreement with those of the authentic compound from ref 3.

Supporting Information Available: ^{1}H NMR of **7**; ^{1}H and ^{13}C NMR spectra for compounds **2**, **4, 5, 8**, **9**, **11**, and an authentic sample **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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