Practical Synthesis of 2-(2-Isopropylaminothiazol-4-yl)-7-methoxy-1*H*quinolin-4-one: Key Intermediate for the Synthesis of Potent HCV NS3 Protease Inhibitor BILN 2061

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Abstract: Herein we describe the development of an efficient, safe and practical process for the synthesis of 7-methoxy-2-(2-amino-4thiazolyl)quinoline. Our new process allowed for a more convergent approach and eliminates the use of potentially dangerous reagents such as diazomethane used in the previous discovery approach.

Key words: BILN2061, protease inhibitor, hepatitis C virus, Sugasawa, quinolone

The selection of HCV (Hepatitis C Virus) protease inhibitor BILN 2061 (1; Scheme 1)³ as a development candidate created the need to establish a suitable synthetic process capable of meeting the drug substance requirements for clinical evaluation, toxicology assessment, formulation and DMPK studies. Accordingly, the need also arose to develop safe, efficient and practical processes for the multi-kilogram synthesis of the different subunits utilized in the assembly of BILN 2061. For example, at the onset of our work there was no synthesis of subunit **3**, and development of an efficient synthetic process for **3** would result in a more convergent approach to BILN 2061 relative to the original discovery route, which employed a more linear route featuring an Arndt–Eistert reaction.⁴ In addition, we sought to eliminate the use of potentially dangerous reagents such as diazomethane used previously for the preparation of the isopropylthiazolylamine group in **1**.⁴ Herein we describe our efforts towards the development of a safe, efficient and practical process for the synthesis of the BILN 2061 hydroxyquinoline/quinolone synthon **3**.⁵

Our retrosynthetic analysis of **3** is shown in Scheme 2. We envisioned the intramolecular cyclization of **4**, which we planned to obtain by the coupling of intermediates **5** and



Scheme 1 Retrosynthetic disconnections for BILN 2061

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Scheme 2 Retrosynthesis analysis for quinolone 3

6. The key to the success of the above strategy was the intramolecular cyclization of aryl amides such as **4**, which is a well-established method for the synthesis of functionalized quinolones.⁶

Thiazole acid **6** was prepared by the condensation of 3bromopyruvic acid (7) and isopropyl thiourea (**8**) as shown in Equation 1.⁷ The above condensation proceeded efficiently to provide **6** as a crystalline solid without the need for purification.





As opposed to the straightforward preparation of 6 described above, the synthesis of 5 required optimization of the reaction conditions. Initially, we studied the modified Friedel–Crafts acylation procedure (AcCl, BCl₃, AlCl₃, CH₂Cl₂) described by Brown and coworkers⁸ for the regioselective acylation of *m*-anisidine (9). After numerous attempts however, we were unable to obtain 5 in the 42% yield reported by Brown.8 Instead, yields of 20-25% were common, and isolation of the product (5) was further complicated by the formation of persistent emulsions during the work-up. We attributed the low yield mainly to the lack of regioselectivity of the reaction that resulted in the formation of undesired regioisomers.9 This lack of regioselectivity, due to the typical tendency of conventional electrophilic aromatic substitution to afford both ortho and para isomers is, in principle, not a problem in the original acylation procedure introduced by Sugasawa, which uses a nitrile as the electrophile. This should result in acylation ortho to the nitrogen via a cyclic transition state in which boron coordinates to both the nitrogen atoms of the aniline and acetonitrile (Equation 2).^{10,11}

Noticeable improvements in the yield of the reaction were indeed realized by simply switching the electrophile from acetyl chloride to acetonitrile. However, the yield of 5 was still moderate (35–40%) due to regioselectivity problems. This lack of regioselectivity in the acylation of *m*-anisidine 9 had also been observed by Sugasawa.¹² In an effort to further improve both the yield and selectivity of the reaction, we screened a variety of reaction conditions for the Sugasawa acylation of 9 (Table 1). The use of $TiCl_4$ or GaCl₃, used successfully by other researchers as AlCl₃ replacements,¹³ failed to improve the yield (entries 1 and 2). Only traces of product were detected when the reaction was carried out at ambient temperature (entry 3), but better results were obtained at reflux in toluene-dichloromethane (50-52 °C) for 15-20 hours (entry 4). Under the above conditions, the selectivity improved to a 4.2:1 mixture of 5 and 10 and the HPLC yield of 5 to 45-55%. A more favorable ratio of 5 to 10 could be obtained by replacing dichloromethane with p-xylene or toluene (entries 5 and 6), but the yield decreased in the absence of dichloromethane. However, using only dichloromethane as the solvent resulted in both a low yield and low selectivity (entry 7). Eventually, in spite of the modest yield, we decided to utilize this reaction in our scale-up process due to its simplicity and the extremely low cost and wide availability of the raw materials.

We were able to isolate rather pure **5** without chromatography. This was accomplished by a suitable work-up/isolation procedure followed by crystallization. More specifically, careful pH control during work-up was required to properly handle the large amounts of inorganic salts present in the crude mixture, eliminate emulsions, and also to remove undesired organic components. In this manner, after the reaction mixture was quenched with isopropanol and water, the pH was slowly adjusted (pH 3) with sodium hydroxide in order to leave the majority of the impurities in the aqueous layer while the desired product (**5**) remained in the organic layer. Further purification was accomplished by crystallization of crude **5** from methyl *tert*-butyl ether (MTBE)/heptanes to afford crystalline material in 40–50% isolated yield.



Equation 2

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Table 1 Synthesis of 5

$MeO = MH_2 \qquad MeO, \\ MeO = MH_2 \qquad MH_$						
Entry	BCl ₃ solvent	Co-solvent	MCl ₃	Temp (°C)	5:10	Yield of 5^{14}
1	CH ₂ Cl ₂	Toluene	TiCl ₄	52	3.3:1	8%
2	CH_2Cl_2	Toluene	GaCl ₃	52	6.7:1	4%
3	CH ₂ Cl ₂	Toluene	AlCl ₃	24	N/A	< 1%
4	CH ₂ Cl ₂	Toluene	AlCl ₃	52	4.2:1	48%
5	<i>p</i> -xylene	Toluene	AlCl ₃	57	7.8:1	20%
6	<i>p</i> -xylene	Toluene	AlCl ₃	80	6.4:1	36%
7	CH ₂ Cl ₂	CH ₂ Cl ₂	AlCl ₃	43	1.4:1	14%

Having established a procedure for the efficient synthesis of **5**, we turned our attention to the following steps for the synthesis of **3**. The coupling of **5** and **6** to give **4** was carried out in a straightforward manner via the acyl chloride of **6** generated upon treatment with oxalyl chloride (Equation 3) followed by addition of **5** and triethylamine. No purification was necessary and crude **4** was used for the subsequent and final step.

For the cyclization of **4** under basic conditions, the choice of solvent was crucial for the overall efficiency of the reaction. The intramolecular cyclization was initially carried out by adding potassium *tert*-butoxide to a solution of **4** in *tert*-butanol, and heating to 75 °C. However, under these conditions, we observed the formation of a sideproduct, which was identified as **11**¹⁵ (Figure 1), and which formed in increased amounts at lower temperatures.¹⁶ Although inverse addition of solid **4** to a hot solution of potassium *tert*-butoxide gave the product in high yield, charging of solids in this way is undesirable in scale-up operations for safety reasons.



Figure 1

To circumvent the above complications, alternative solvents were tested in place of tetrahydrofuran-*tert*-butanol and the best results were obtained with 1,2-dimethoxy-ethane as the solvent (Equation 4). Accordingly, the reaction was carried out by adding a solution of 4 in 1,2-dimethoxyethane to a refluxing solution of potassium *tert*-butoxide also in 1,2-dimethoxyethane, followed by quenching with aqueous acid. Furthermore, the controlled addition of aqueous acid resulted in precipitation of the product, which was collected by filtration without the need for work-up or further purification. Under the above conditions, the isolated yield of 3 increased to 82%, and formation of 11 was not observed even when the temper-



Equation 4

Equation 3

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ature was purposely allowed to decrease to 50 $^{\circ}$ C in control experiments, confirming the decisive role of 1,2-dimethoxyethane in directing the reaction to the exclusive formation of **3**.

In conclusion, we have developed a practical, safe, robust and economic process for the synthesis of **3**, which is a key intermediate in the synthesis of the HCV protease inhibitor BILN 2061. Our process is highly convergent and eliminates the use of potentially dangerous reagents such as diazomethane used in the original discovery route. No practical preparation for this compound (**3**) existed before our work and considerable process research work, especially the optimization of the Sugasawa acylation of **9** and the intramolecular cyclization of **4**, was carried out. Development of the above process for the synthesis of **3** allowed for the subsequent preparation of **1** in multikilogram amounts for toxicology, formulation and clinical studies.¹⁷

Unless otherwise specified, all reactions were carried out in ovendried glassware under an atmosphere of nitrogen. NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane; coupling constants (*J*) are reported in hertz, and refer to apparent peak multiplicities, and may not necessarily be true coupling constants. The commercially available starting materials were used as received without further purification and all solvents were dried by standard methods prior to use. All melting points are recorded using a Fisher–Johns melting point apparatus and are uncorrected.

2-Isopropylaminothiazole-4-carboxylic Acid Hydrobromide (6) Pyruvic acid (5.00 g, 56.8 mmol) was charged into a 250 mL flask equipped with mechanical stirrer, condenser and N₂ inlet, and bromine (9.07 g, 56.8 mmol) was added dropwise, allowing each drop to decolorize between additions. The temperature of the reaction was allowed to rise spontaneously to 40–50 °C. After completion of the addition, the mixture was stirred for an additional 5 min and then diluted with dioxane (125 mL). Isopropyl thiourea (6.70 g, 56.8 mmoL) was added all at once and the slurry was refluxed for 1 h. After cooling, the precipitate was filtered and washed with Et₂O, then dried in vacuo to afford the product (11.3 g, 75%) as a white solid; mp 191–192 °C.

¹H NMR (400 MHz, DMSO- d_6): δ = 1.18 (d, J = 6.4 Hz, 6 H), 3.97 (m, 1 H), 7.60 (s, 1 H), 9.20 (br, 1 H).

¹³C NMR (100 MHz, DMSO- d_6): $\delta = 21.8$, 48.1, 117.2, 133.5, 159.2, 167.1.

Anal. Calcd for C₇H₁₁BrN₂O₂S: C, 31.47; H, 4.15; N, 10.49. Found: C, 31.47; H, 4.02; N, 10.38.

1-(2-Amino-4-methoxyphenyl)ethanone (5)

BCl₃ (801 mL of a 1 M solution in CH₂Cl₂, 800.6 mmol) was added dropwise to a solution of anisidine (**5**; 90.0 mL, 800.6 mmol) and toluene (506 mL) over a period of 2 h, keeping the internal temperature at 0–5 °C. MeCN (50.2 mL, 961 mol) was then added at 0–5 °C over a period of 20 min and the mixture was stirred for 40 min. Solid AlCl₃ (117 g, 881 mmol) was charged in one portion at 0–5 °C, the mixture was stirred for 5–10 min and heated to reflux (50– 51 °C). The mixture was kept at reflux for 12–16 h, cooled to 0 °C and quenched by adding *i*-PrOH (370 mL) over a period of 30 min. H₂O (1.06 L) was then added over a period of 50 min, keeping the temperature at 10 °C. The mixture was then stirred at reflux for 3 h (50 °C) and allowed to reach ambient temperature. The pH of the aqueous solution was adjusted to 3 with 25% aq NaOH (125 mL). The organic portion was collected and the aqueous layer was extracted with toluene (3×500 mL). The combined organic portions were washed sequentially with 12.5% NaOH (600 mL) and H₂O (600 mL). Concentration under reduced pressure (rotary evaporator, 40 °C) afforded a brown solid. MTBE (322 mL) was added and the mixture was heated to reflux (57–59 °C). Heptane (158 mL) was then added over a period of 15 min. The mixture was heated to reflux (66–69 °C) for 1 h and then stirred at ambient temperature for 8–12 h. The resulting solid was collected by filtration at 10 °C and washed with heptane (100 mL) to afford a light brown solid (55.4 g, 42%) after drying. NMR spectral data of the above product was consistent with literature values.⁸

2-Isopropylaminothiazole-4-carboxylic Acid (2-Acetyl-5-methoxyphenyl)amide (4)

Oxalyl chloride (6.97 mL, 79.9 mmol) was added dropwise to a stirred solution of **6** (21.3 g, 79.9 mmol), DMF (0.2 mL) and CH₂Cl₂ (144 mL) at 5 °C over a period of 10 min. The mixture was then stirred at 25 °C for 1 h. The resulting solution was cooled again to 5 °C and solid **5** (12.0 g, 72.6 mmol) was added in four portions over a period of 1 h. The mixture was stirred for 30 min at 25 °C and Et₃N (40.5 mL, 291 mmol) was added at 10 °C over a period of 20 min. The mixture was stirred at 25 °C for 1.5 h and quenched with sat. aq NaHCO₃. The organic portion was collected, washed with H₂O (2 × 100 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford **4** (24.3 g; 100% crude yield) as a yellow solid. An analytical sample was purified by crystallization from CH₂Cl₂–hexanes to afford a pale-yellow solid.

¹H NMR (400 MHz, CDCl₃): δ = 1.34 (d, *J* = 6.4 Hz, 6 H), 2.63 (s, 3 H), 3.77 (m, 1 H), 3.91 (s, 3 H), 5.26 (br d, *J* = 7.7 Hz, 1 H), 8.65 (d, *J* = 2.6 Hz, 1 H), 6.64 (dd, *J* = 2.6, 9.0 Hz, 1 H), 7.42 (s, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 13.13 (br s, 1 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 22.6, 28.1, 47.9, 55.4, 104.1, 109.7, 112.5, 116.0, 133.4, 143.2, 146.7, 161.0, 164.3, 167.8, 200.2. Anal. Calcd for C₁₆H₁₉N₃O₃S: C, 57.64; H, 5.74; N, 12.60. Found: C, 57.54; H, 5.58; N, 12.49.

2-(2-Isopropylaminothiazol-4-yl)-7-methoxy-4a,8a-dihydro-1*H*-quinolin-4-one (3)

Solid *t*-BuOK (26.93 g, 240.0 mmol) was charged into a dry threeneck flask followed by anhyd DME (260 mL) and the resulting mixture was heated to reflux (87–89 °C). A solution of amide **4** (20 g, 60.0 mmol) and DME (120 mL) was then slowly added to the above refluxing solution over a period of approximately 1 h. Upon complete addition of **7**, the mixture was held at reflux for an additional 15–20 min and then allowed to cool to 22–25 °C. HCl (1 N, 221 mL) was added slowly over a period of 1 h, keeping the internal temperature at 22–25 °C until the solution was neutral (pH 7). The resulting slurry was stirred at 22–25 °C for 3 h and then H₂O (300 mL) was added slowly over a period of 1 h. The slurry was stirred at ambient temperature for 4–12 h and the resulting solid was collected by filtration to afford the product (18.0 g, 82% yield) as a tan solid; mp 245–247 °C.

¹H NMR (400 MHz, DMSO- d_6): $\delta = 1.22$ (d, J = 6.5 Hz, 6 H), 3.87 (s, 3 H), 3.98 (m, 1 H), 6.52 (d, J = 1.6 Hz, 1 H), 6.89 (dd, J = 2.3, 8.9 Hz, 1 H), 7.28 (d, J = 2.3 Hz, 1 H), 7.50 (s, 1 H), 7.76 (d, J = 7.6 Hz, 1 H), 7.95 (d, J = 8.9 Hz, 1 H), 11.04 (s, 1 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 22.3, 46.2, 55.4, 99.6, 105.6, 106.7, 113.1, 119.5, 126.4, 141.8, 143.5, 144.0, 161.9, 167.6, 176.7.

HRMS (APCI): m/z calcd for $C_{16}H_{18}N_3O_2S$: 316.1114; found: 316.1112.

Anal. Calcd for $C_{16}H_{17}N_3O_2S$: C, 60.93; H, 5.43; N, 13.32. Found: C, 60.89; H, 5.34; N, 13.26.

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References

- Present Address: Johnson and Johnson Pharmaceutical Research and Development, Turnhoutseweg 30, 2340 Beerse, Belgium.
- (2) Present Address: Battelle, 505 King Avenue, Columbus, Ohio 43201, USA.
- (3) (a) Lamarre, D.; Anderson, P. C.; Bailey, M.; Beaulieu, P.; Bolger, G.; Bonneau, P.; Boes, M.; Cameron, D. R.; Cartier, M.; Cordingley, M. G.; Faucher, A.-M.; Goudreau, N.; Kawai, S. H.; Kukolj, G.; Lagace, L.; LaPlante, S. R.; Narjes, H.; Poupart, M.-A.; Rancourt, J.; Sentjens, R. E.; St. George, R.; Simoneau, B.; Steinmann, G.; Thibeault, D.; Tsantrizos, Y. S.; Weldon, S. M.; Yong, C.-L.; Llinàs-Brunet, M. *Nature (London)* 2003, *426*, 186. (b) Llinàs-Brunet, M.; Bailey, M.; Bolger, G.; Brochu, C.; Faucher, A.-M.; Ferland, J.-M.; Garneau, M.; Ghiro, E.; Gorys, V.; Grand-Maître, C.; Halmos, T.; Lapeyre-Paquette, N.; Liard, F.; Poirier, M.; Rhéaume, M.; Tsantrizos, Y. S.; Lamarre, D. *J. Med. Chem.* 2004, *47*, 1605.
- (4) Faucher, A.-M.; Bailey, M. D.; Beaulieu, P. L.; Brochu Duceppe, J.-S..; Ferland, J.-M.; Ghiro, E.; Gorys, V.; Halmos, T.; Kawai, S. H.; Poirier, M.; Simoneau, B.; Tsantrizos, Y. S.; Llinàs-Brunet, M. Org. Lett. 2004, 6, 2901.
- (5) For an alternative approach to 3 via a carbonylative Sonogashira coupling–cyclization see: Haddad, N.; Tan, J.; Farina, V. J. Org. Chem. submitted for publication.
- (6) For additional examples of similar cyclizations to prepare quinolones, see: (a) Combs, D. W.; Reed, M. S.; Klaubert, D. H. Synth. Commun. 1992, 22, 323. (b) Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-S.; Lednicer, D.; Lin, C. M.; Hamel, E.; Lee, K.-H. J. Med. Chem. 1994, 37, 1126. (c) Fuerstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. J. Org. Chem. 1994, 59, 5215. (d) Li, L.; Wang, H.-K.; Kuo, S.-C.; Wu, T.-S.; Mauger, A.; Lin, C. M.; Hamel, E.; Lee, K.-H. J. Med. Chem. 1994, 37, 3400. (e) Mahboobi, S.; Pongratz, H. Synth. Commun. 1999, 29, 1645. (f) Traxler, P.; Green, J.; Mett, H.; Séquin, U.; Furet, P. J. Med. Chem. 1999, 6, 1018. (g) Takami, H.; Kishibayashi, N.; Ishii, A.; Kumazawa, T. Bioorg. Med. Chem. 1998, 6, 2441. (h) Haesslein, J.-L.; Baholet, I.; Fortin, M.; Iltis, A.; Khider, J.; Periers, A. M.; Pierre, C.; Vevert, J.-P. Bioorg. Med. Chem. Lett. 2000, 10, 1487. (i) Beney, C.; Hadjeri, M.; Mariotte, A.-M.; Boumendjel, A. Tetrahedron Lett. 2000, 41, 7037. (j) Niedzinski, E. J.; Lashley, M. R.; Nantz, M. H. Heterocycles 2001, 55, 623.

- (7) For additional examples of thiazoles prepared from 3bromopyruvic acid in a similar fashion, see: (a) Kelly, T. R.; Echavarren, A.; Chandrakumar, N. S.; Koeksal, Y. *Tetrahedron Lett.* **1984**, 25, 2127. (b) Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409.
- (8) Brown, F. J.; Bernstein, P. R.; Cronk, L. A.; Dosset, D. L.; Hebbel, K. C.; Maduskuie, T. P. Jr.; Shapiro, H. S.; Vacek, E. P.; Yee, Y. K.; Willard, A. K.; Krell, R. D.; Snyder, D. W. *J. Med. Chem.* **1989**, *32*, 807.
- (9) Water-soluble side-products from the reaction mixture were not isolated, but most likely a major side-product was 4-amino-2-hydroxyacetophenone. For leading references on the related formation of 4-acetamido-2-hydroxyacetophenone by Friedel–Crafts acylation/demethylation of 4-acetamido-2-methoxyacetophenone and similar reactions, see: (a) Gibson, C. S.; Levin, B. J. Chem. Soc. 1931, 2388. (b) Chen, F. C.; Chang, C. T. J. Chem. Soc. 1958, 146. (c) Cignarella, G.; Barlocco, D.; Curzu, M. M.; Pinna, G. A.; Cazzulani, P.; Cassin, M.; Lumachi, B. Eur. J. Med. Chem. 1990, 25, 749.
- (10) (a) Sugasawa, T.; Toyoda, T.; Adachi, M.; Sasakura, K. J. Am. Chem. Soc. 1978, 78, 4842. (b) Douglas, A. W.; Abramson, N. L.; Houpis, I. N.; Karady, S.; Molina, A.; Xavier, L. C.; Yasuda, N. Tetrahedron Lett. 1994, 35, 6807.
- (11) For recent mechanistic studies and industrial application of the Sugasawa reaction, see: Prasad, K.; Lee, G. T.; Chaudhary, A.; Girgis, M. J.; Streemke, J. W.; Repič, O. *Org. Process Res. Dev.* **2003**, *7*, 723.
- (12) Sugasawa, T.; Adachi, M.; Sasakura, K.; Kitagawa, A. J. Org. Chem. **1979**, 44, 578.
- (13) Houpis, I. N.; Molina, A.; Douglas, A. W.; Xavier, L.; Lynch, J.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* 1994, *35*, 6811.
- (14) The yield was determined by a quantitative HPLC assay.
- (15) 2-Isopropylamino-7-methoxy-4-methylene-4,9-dihydro-3thia-1,9-diazabenz[*f*]azulen-10-one (**11**): ¹H NMR (400 MHz, DMSO-*d*₆): $\delta = 1.14$ (d, J = 6.4 H, 6 H), 3.72 (s, 3 H), 3.70–3.85 (m, 1 H), 5.30 (s, 1 H), 5.34 (s, 1 H), 6.70–6.75 (m, 2 H), 6.75 (d, J = 2.4 Hz, 1 H), 7.28 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 7.5 Hz, 1 H), 10.0 (s, 1 H). ¹³C NMR (100 MHz, DMSO-*d*₆): $\delta = 22.7$, 46.3, 55.7, 106.4, 110.6, 116.8, 123.1, 130.1, 131.5, 137.0, 139.6, 160.2, 161.4, 163.9.
- (16) Up to 50% of **11** was formed when the reaction was carried out at 50 °C. Electrophilic reaction of 2-aminothiazoles at C-5 is well precedented. In this case, it may be promoted by ionization of the C-2 isopropylamino group, although usually strong bases like sodium amide have been employed to obtain deprotonation at such amino groups. See: *Heterocyclic Compounds*; Weissberger, A.; Taylor, E. C., Eds.; Wiley: New York, **1979**.
- (17) A manuscript describing the complete assembly of BILN 2061 using 3 is in preparation and will be published in due course.