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Solid Phase Synthesis of 1,3,5-Trisubstituted Pyridin-2-ones

James A. Linn*, Samuel W. Gerritz, Anthony L. Handlon, Clifton E. Hyman, Dennis Heyer
Glaxo Wellcome Research and Development
Five Moore Drive, Research Triangle Park, NC 27709

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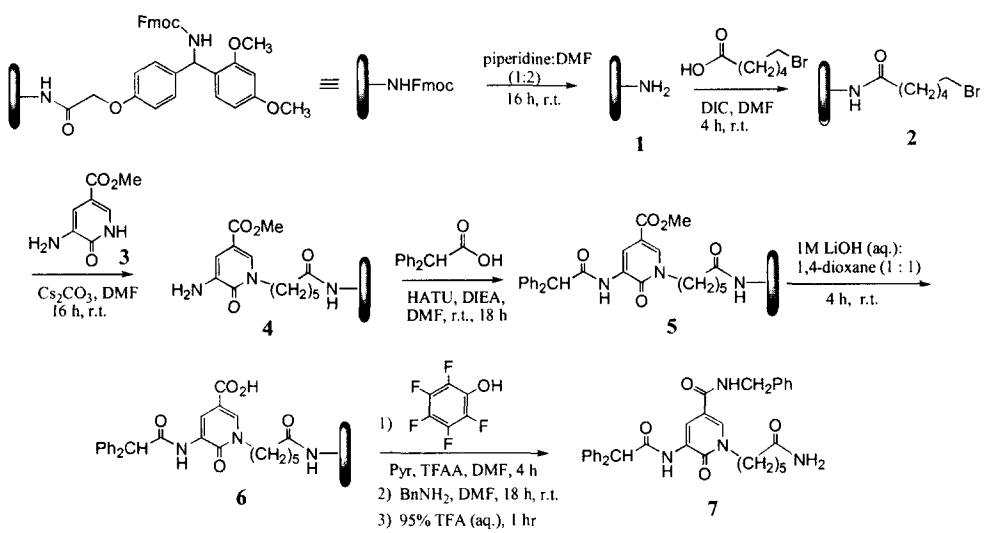
Abstract: The solid phase synthesis of 1,3,5-trisubsituted pyridin-2-ones is reported via selective ^{1}NH- alkylation of 3-amino-5-carbomethoxy-1H-pyridin-2-one with a solid-supported halo-acid. Coupling of an acid to solid-supported 3-aminopyridinone was followed by saponification of the methyl ester to give the acid. Activation of the acid via the pentafluorophenyl ester allowed reaction with an amine, and cleavage from the solid support with TFA:H_2O (95:5) provided 1,3,5-trisubstituted pyridin-2-ones.

Substituted pyridinones have been found to exhibit a wide range of biological activities. These include cardiovascular activities as with antithrombotics[1a-b] and angiotensin II receptor antagonists,[1c] and anti-infective activities as with HIV-reverse transcriptase inhibitors,[1d-e] anthelmintics,[1f] and antibacterials.[1g] In addition, pyridinones have been shown to exhibit anti-cancer/anti-tumor[1h-i] activity, and inhibit tumor necrosis factor-α[1j] and 5α-reductase.[1k] As a result of these interesting biological activities, we became focused on developing a library of substituted pyridin-2-ones using a solid phase synthesis. Although the solution phase literature of pyridin-2-ones[2a-d] is extensive, there has been only one report of a solid-phase synthesis of a related, albeit different, dihydropyridone scaffold.[3] In our case, diversity was incorporated onto the pyridinone scaffold using three sets of monomers appended to the lactam ^{1}NH, 3-amino and 5-carboxy groups.

Scheme 1



The solid phase synthesis of pyridin-2-ones commenced with deprotection of the Fmoc-protected Rink linker-equipped Chiron macrocrowns[4] using piperidine:DMF (1:2) to give **1**. The 6-bromohexanoic acid was coupled to the Rink amine macrocrown using diisopropylcarbodiimide (DIC) in DMF. The resulting solid-supported 6-

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bromohexanamide, **2**, was used to alkylate 3-amino-5-carbomethoxy-1H-pyridin-2-one,[5] **3**, using Cs_2CO_3 in DMF. Alkylation of **3** proceeded chemoselectively at the lactam ^{1}NH. The coupling of diphenylacetic acid to **4** was done using O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU) and N,N-diisopropyl-ethylamine (DIEA) in DMF which gave methyl ester **5**. Saponification of the ester with 1M aqueous lithium hydroxide:1,4-dioxane (1:1) provided the solid-supported carboxylic acid, **6**, after washing with 1N hydrochloric acid (aqueous):THF (1:1) to liberate the free acid. Treatment of carboxylic acid **6** with pentafluorophenol and pyridine in DMF, followed by addition of neat trifluoroacetic anhydride to the macrocrown mixture gave the pentafluorophenyl (pfp) ester in situ. The solid-supported pfp-ester was treated with benzylamine in DMF and after appropriate washing the product was cleaved from the macrocrown using TFA:H_2O (95:5) for 1 hr. to give pyridinone **7**.[6,7]

Intermediates **4**, **5** and **6** were each cleaved from macrocrowns with TFA:H_2O (95:5) for 1 hr to determine completeness of reaction and purity. After concentrating to dryness the residues were characterized by LC-MS, analytical HPLC and ^{1}H-NMR. Pfp-ester formation was initially examined using a modification of a solution phase procedure.[8] Commercially available pentafluorophenyl trifluoroacetate[9] proved to be a useful reagent for generating the pfp-ester on a small scale using only a few macrocrowns, but it was deemed too costly to use on a production scale. The use of the less expensive pentafluorophenol and TFAA proved to be a valuable alternative for preparing the pfp-ester on solid support during full library production. In should be noted that pfp-ester *formation* was found to be sensitive to moisture, although the pfp-ester once formed was stable even to the cleavage conditions using TFA:H_2O (95:5).

The scope and limitations of each monomer set are summarized here. For the M1 set of halo-acids: bromoacetic, 3-bromopropanoic, 4-bromobutyric, and N-chloroacetyl-protected amino acids did not work well, presumably because of inefficient coupling of the halo-acid to the macrocrown Rink amine. The lack of an observable M+1 signal in the mass spectrum after reaction of the solid-supported halide with piperidine, followed by cleavage of the product from the solid support using TFA:H2O (95:5), provided indirect evidence for the poor coupling efficiencies seen in these cases. Various 'endcapping groups' of a M2 set of monomers were used to acylate the 3-aminopyridinone, **4**. However, it was found that isocyanates, isothiocyanates, chloroformate esters, acid chlorides, sulfonyl chlorides, and sulfamoyl chlorides reacted poorly and gave little or no acylated product. Only the coupling of M2 acids using HATU gave desired products in many cases. Substituted benzoic, hindered alkanoic, 2-thiophenoic, and oxamic acids did not couple well. However, 2-furanoic, diphenylacetic and nicotinic acids coupled well. Amines from the M3 monomer set which gave poor results in the reaction with the pfp-ester were many alkyl diamines (with at least one primary amine present), furfurylamine, hydroxy-, methoxy- and benzyloxyamine, norbornylamine, and bulky hindered amines like 2,2-diphenylethylamine. Interestingly, a few diamines such as piperazine, 2,5-diazahexane and 2,6-diazaheptane gave good results.

In summary, we have described the use of a pyridin-2-one scaffold to construct a library of 1,3,5-trisubstituted pyridinones using macrocrowns as a solid support. Methodology has been described to prepare a key intermediate pfp-ester using pentafluorophenol and TFAA, or alternatively with pentafluorophenyl trifluoroacetate. Although numerous solid phase methods are reported for amide bond forming reactions, few methods describe activation of a solid-supported acid towards coupling with amines. The pfp-ester approach described here supplements the array of solid phase chemistries now available to chemists.

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4. Macrocrowns were purchased from Chiron Mimotopes Pty. Ltd., Clayton, Victoria, Australia.
5. Intermediate **3** was synthesized in three steps from commercially available 6-hydroxynicotinic acid. First, 6-hydroxynicotinic acid (50 g) was nitrated with red fuming HNO_3 (400 mL) at 70-80°C for 9 hr, then cooled to ambient temperature overnight to give 23 g of precipitated 6-hydroxy-5-nitronicotinic acid. The mother liquor was reduced to dryness to give 20 g of a mixture of starting material to product (2:1). This was added to 50 g of 6-hydroxynicotinic acid and the mixture nitrated with red fuming HNO_3 (300 mL) to give 41 g of precipitated 6-hydroxy-5-nitronicotinic acid: total yield, 64 g (48%) of 6-hydroxy-5-nitronicotinic acid. This product was esterified in two stages (one pot) by treating a stirred mixture of 6-hydroxy-5-nitronicotinic acid (64 g), pyridine (0.14 mL, 0.005 eq.) and CH_3CN (500 mL) at 80°C with addition of $SOCl_2$ (51 mL, 2.0 eq.). The mixture was refluxed for 2 hr until all solids were in solution. A solution of Et_3N (97 mL, 2.0 eq.) in MeOH (400 mL) was cautiously added dropwise. After addition was completed, heating was stopped and the reaction was stirred at ambient temperature for 2 hr. The volatiles were removed in vacuo and the residual paste was treated with 1N HCl (250 mL) with stirring. The mixture was chilled on ice, solids collected, and then dried at 75°C for 24 hr. to give 55 g (74%) of 5-carbomethoxy-3-nitro-1H-pyridin-2-one. The 5-carbomethoxy-3-nitro-1H-pyridin-2-one (10 g) was reduced catalytically using 10% Pd/C (1.0 g) under a H_2 atmosphere in 95% EtOH (500 mL) for 5 hr. Fresh catalyst (0.5 g) was added to the reaction mixture and the reduction continued for 18 hr. more. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a quantitative yield of the 3-amino-5-carbomethoxy-1H-pyridin-2-one (8.5 g). ^{1}H-NMR and electrospray (+)-ion mass spectral data were consistent with the structure.
6. Experimental procedure for the synthesis of **7**: To an fmoc-protected Rink-equipped MA/DMA macrocrown (loading: 7.2 μmoles) in a glass vial was added 0.5 mL of piperidine:DMF (1:2) and the mixture shaken overnight for 20 hr. The crown was filtered and washed with DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). To the fmoc-deprotected Rink-amine macrocrown in a glass vial was added 0.5 mL of a 1M solution of 6-bromohexanoic acid in DMF followed by 0.5 mL of a 1M solution of diisopropylcarbodiimide in DMF and the resulting suspension was shaken overnight for 22 hr. The crown was filtered and washed with DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). The crown was added to a mixture of **3** (21mg), Cs_2CO_3 (43 mg) and DMF (0.5 mL) and the mixture shaken overnight for 18 hr. The crown was filtered and washed with water (1 x 1 mL), then DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). Next, the crown was placed in a glass vial containing 2,2-diphenylacetic acid (12 mg), DIEA (58 μL), and DMF (0.44 mL). After shaking for 10 min. a solution of HATU (38 mg) in DMF (0.5 mL) was added to the macrocrown mixture and the reaction shaken overnight for 20 hr. The crown was filtered and washed with DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). The crown was then added to a mixture of 1M LiOH (aq.) (0.5 mL) and 1,4-dioxane (0.5 mL) and the mixture shaken for 4 hr. The crown was filtered and washed (3x) with 1N HCl:THF (1:1), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). The crown was then dried at 75°C under vacuum for 18 hr. The crown was then placed in a glass vial containing pentafluorophenol (46 mg), pyridine (40 μL), and DMF (0.42 mL). Next, trifluoroacetic anhydride (35 μL) was added to the crown mixture and the reaction shaken for 4 hr. The crown was filtered and

then washed with DMF (1 x 1 mL), THF (1 x 1 mL) and CH_2Cl_2 (1 x 1 mL). The pfp-ester forming reaction was repeated on the crown using the above identical conditions ('double couple'). The crown was filtered and then washed with DMF (1 x 1 mL), THF (1 x 1 mL) and CH_2Cl_2 (1 x 1 mL). The crown was placed in a glass vial containing a solution of benzylamine (27 μL) in DMF (0.47 mL) and the mixture was shaken for 18 hr. The crown was filtered and washed with DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). Finally, the crown was placed in a glass vial and treated with TFA(0.95 mL):H_2O (0.05 mL) for 1 hr. The crown was removed and the resulting solution was concentrated *in vacuo* to provide pyridinone **7** (3.7 mg, >93% crude yield). The crude material was 90% pure by reversed-phase HPLC [Waters Delta Pak® 5μ C18 300A column (3.9 x 150 mm) , 1.5 mL/min flow rate, 10% CH_3CN/H_2O to 90% CH_3CN/H_2O (0.1% TFA) gradient over 20 min.].

7. Compound **7**: ^{1}H-NMR (DMSO-d_6): δ (ppm) 9.65 (s, 1H, 3-NHC(O)), 8.80 (t, J = 5.9 Hz, 1H, 5-C(O)NH), 8.70 (d, J = 2.4 Hz, 1H, pyridinone H-6), 8.08 (d, J = 2.1 Hz, 1H, pyridinone H-4), 7.5-7.2 (m, 15H, ArH), 7.3/6.7 (2 x br s, 2H, $C(O)NH_2$), 5.65 (s, 1H, $CH(Ph)_2$), 4.40 (d, J = 5.8 Hz, 2H, NCH_2Ph), 3.94 (t, J = 7.2 Hz, 2H, $^1NCH_2$), 2.00 (t, J = 7.3 Hz, 2H, $CH_2C(O)$), 1.64/1.46/1.22 (3 x m, J = 6.6-7.4 Hz, 6H, 3 x CH_2). Mass spectrum showed MH^+ 551 m/z for the major peak.
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9. Alternatively, the pfp-ester was prepared from **6** using commercially available pentafluorophenyl trifluoroacetate. The macrocrown was first dried at 75°C under vacuum for several hours. The crown was then placed in a dried glass vial containing dry pyridine (19 μL), and DMF (0.44 mL). Next, pentafluorophenyl trifluoroacetate (43 μL) was added to the crown mixture and the reaction shaken for 4 hr. The crown was filtered and then washed with DMF (1 x 1 mL), THF (1 x 1 mL) and CH_2Cl_2 (1 x 1 mL). The pfp-ester forming reaction was repeated on the crown using the above identical conditions ('double couple'). The crown was filtered and then washed with DMF (1 x 1 mL), THF (1 x 1 mL) and CH_2Cl_2 (1 x 1 mL). The crown was placed in a glass vial containing a solution of benzylamine (27 μL) in DMF (0.47 mL) and the mixture was shaken for 18 hr. The crown was filtered and washed with DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). Finally, the crown was placed in a glass vial and treated with TFA(0.95 mL):H_2O (0.05 mL) for 1 hr. The crown was removed and the resulting solution was concentrated *in vacuo* to provide pyridinone **7** (3.6 mg, >90% crude yield). The crude material was 92% pure by reversed-phase HPLC. The mass spectrum and ^{1}H-NMR were identical to **7** prepared from the TFAA experiment described in ref. 6.