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Early Amidation Approach to 3-[(4-Amido)pyrrol-2-yl]-2-indolinones†

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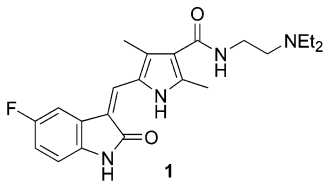
Abstract: A new synthesis of 3-[(4-amido)pyrrol-2-yl]-2-indolinones has been developed, where the amide side chain was installed prior to pyrrole formation. This strategy precludes the need to use any coupling reagents to install the amide side chain. This process includes a zinc-free alternative to the Knorr pyrrole synthesis.

A number of indolinone derivatives have been known to exhibit pharmaceutical activity. Specifically, compounds containing an amide group on a heterocyclic ring condensed with the indolinone have been shown to modulate protein kinase activity. Such compounds could possibly be used to treat a variety of conditions such as various types of cancer, mastocystosis, allergy associated chronic rhinitis, diabetes, arthritis, angiogenesis, immunological and cardiovascular disorders, etc. Of this class of compounds, **1** is being investigated in phase I/II clinical trials in cancer.[1]



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The first-generation synthesis of this compound utilized the approach depicted in Scheme 1 where the pyrrole core was assembled via a Knorr pyrrole reaction between oxime **3** and ethyl acetoacetate (**4**).[2] *tert*-Butyl acetoacetate **2** was treated with $NaNO_2$/HOAc to give the corresponding oxime **3**, which was allowed to react with ethyl acetoacetate **4** in the presence of zinc under the classical Knorr pyrrole reaction conditions to furnish pyrrole **5**. This compound underwent facile decarboxylation upon treatment with HCl to give the α-free pyrrole **6**. Vilsmeier formylation followed by hydrolysis of the ethyl ester gave the key acid−aldehyde **7**.[3] This was then coupled with excess diamine **8** using CDI (carbonyl diimidazole), leading to the imine−amide intermediate **9**. Addition of 5-fluorooxindole **10** to the crude reaction mixture led to the target molecule.

The approach described in Scheme 1 relied on a late-stage coupling of the pivotal pyrrole core **7** with diamine **8** and 5-fluorooxindole **10**. An advantage of this strategy was that it rendered the process amenable to the rapid synthesis of several analogues. One could imagine treating pyrrole **7** with a variety of amines and substituted oxindoles to afford a host of indolinones. However, this approach had two important limitations from the standpoint of commercial process development for compound **1**. The amidation reaction had to be performed on an activated carboxylic acid derivative. In such an event, the presence of the aldehyde moiety led to the formation of the imine in addition to the desired amide. While the imine itself did not pose problems in the subsequent aldol coupling step, its formation necessitated the use of excess diamine in the amide formation step. This, although acceptable in the case of inexpensive amines, was an issue when more expensive amines were involved. Subsequent removal of the excess amine could also prove problematic. Moreover, of the several known amide coupling reagents, very few (such as EDC and CDI) gave satisfactory results. Removal of the byproducts (arising from the activating agent) from these coupling reactions could be problematic and should be carefully considered while developing workup conditions. The use of these activating agents was also undesirable from an atom economy standpoint, since no portion of the reagent was incorporated in the final molecule. These limitations prompted us to examine alternate approaches to the target compound.

We envisioned that the issue of excess diamine could be resolved if one were to install the aldehyde moiety after amide bond formation. Our new retrosynthetic analysis is presented in Scheme 2, whereby the pyrrole core may be assembled with the amide chain in place. To synthesize pyrrole **11** via the Knorr reaction, one would have to start from oxime **3** (derived from *tert*-butyl acetoacetate) and β-ketoamide **12**. This compound can be made from diketene **13** and *N*,*N*-diethylethylenediamine **8**. This approach would circumvent the need to use excess amine, as well as amide coupling reagents. Our results are discussed below.

Treatment of diketene with *N*,*N*-diethylethylenediamine in *tert*-butyl methyl ether furnished β-ketoamide **12** in excellent yield (Scheme 3).[4] The β-ketoamide was prone to decomposition and, therefore, had to be either used immediately or stored at −20 °C. The product was typically contaminated with polymeric material that carried over from diketene. However, this did not cause any problems in the downstream chemistry. Oxime **3**, derived from *tert*-butyl acetoacetate, was treated with

† This paper is dedicated to the memory of Dr. Thomas J. Fleck.

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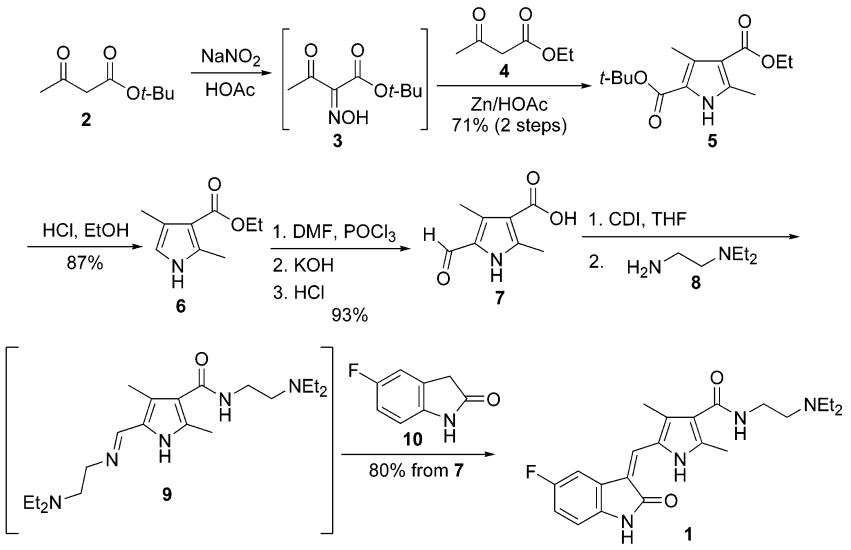
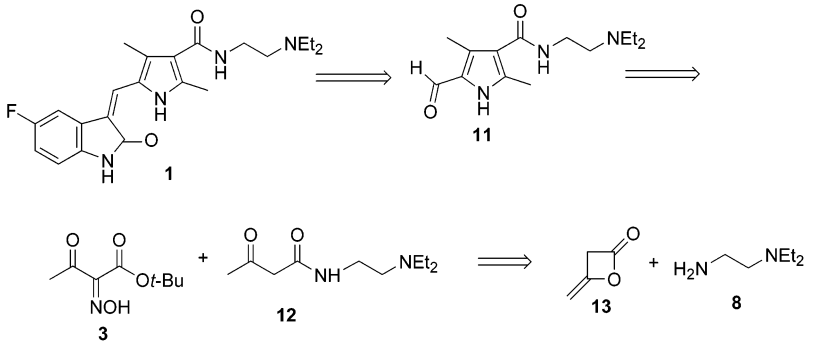
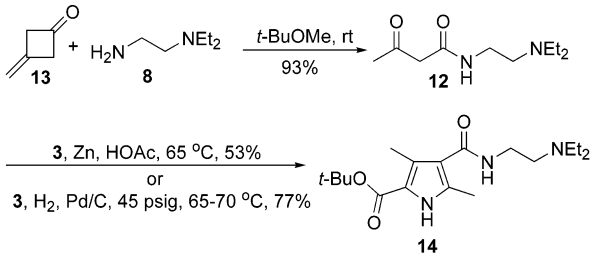
SCHEME 1



SCHEME 2



SCHEME 3



amide **12** in the presence of zinc and acetic acid according to the classic Knorr pyrrole formation conditions, which led to pyrrole **14**. On a small scale, this reaction worked fairly well (> 60% yield). However, as the reaction scale was increased, workup proved problematic. Typically, the products of Knorr reactions (when β-ketoesters are used) are isolated by a water knock-out.[2] In our case, the presence of an extra amine functionality in **14** rendered precipitation of the product from an acidic reaction mixture impossible. The mixture had to be basic for the product to precipitate out; unfortunately, at pH 9, zinc salts crashed out of solution, making an extraction or isolation extremely difficult. Attempts to filter off the zinc salts before proceeding with the extractive workup proved disastrous. The workup problem was minimized by adding CH_2Cl_2 to the reaction mixture at the end of the pyrrole formation reaction, followed by basification with 50% NaOH until the pH was 13−14. The zinc salts that formed at pH 9 dissolved at pH 13−14. A series of water−CH_2Cl_2 extractions led to the isolation of the product in 53% yield. Although this strategy worked well, we still had to go through pH 9 to reach pH 13! In other words, there was no way to avoid precipitation of zinc salts, although they could be dissolved later. We believed that such gelatinous salts could cause further complications during scale-up (like binding the agitator) and sought other alternatives to the zinc chemistry. The environmental concerns associated with the use and disposal of stoichiometric zinc was another important factor in our inclination to pursue other options.

One attractive alternative to the zinc chemistry was to use hydrogenation conditions to form the pyrrole core. Oxime reduction[5] and pyrrole synthesis[6] using hydrogenation conditions are well-known in the literature; however, there are very few reports of Knorr synthesis of pyrroles bearing amide side chains under hydrogenation conditions.[7] To our delight, hydrogenation of a mixture of amide **12** and oxime **3** over 10 wt % Pd/C catalyst in acetic acid (45 psig, 65−70 °C, 7 h) led to the

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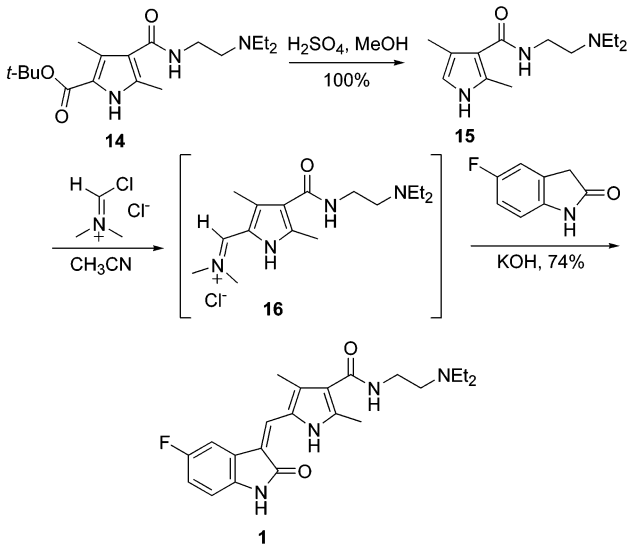
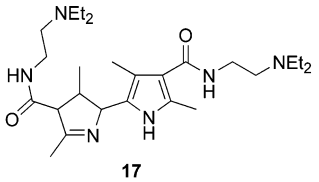
SCHEME 4



clean formation of pyrrole **14**. The reaction workup was extremely simple—the catalyst was filtered off, and the filtrate was basified to pH 11−13 and extracted with CH_2Cl_2 to afford the product in 77% yield. These results demonstrated that the hydrogenation procedure was a viable alternative to the zinc protocol, especially for compounds that cannot be extracted or precipitated under acidic conditions.

Having assembled the pyrrole core, we endeavored to attach the oxindole side chain and complete the synthesis. We envisioned that the previously noted decarboxylation conditions (HCl/EtOH) used to convert **5** to **6** could be extrapolated to the current synthesis. However, in this case, when HCl was used, the decarboxylated product **15** was obtained in good yield, but dimer **17** was also formed. It was found that this impurity was formed early in the reaction and increased over time. Several acids were screened to see if the decarboxylation could be effected cleanly. We discovered that the use of 1 M H_2SO_4 in MeOH (3:1 in H_2O) at 65 °C led to clean decarboxylation without any trace of the undesired byproduct.[8] The use of TFA at lower temperature also gave satisfactory results. The α-free pyrrole thus obtained (**15**) was treated with chloromethylenedimethylammonium chloride in acetonitrile to form the Vilsmeier adduct **16** in situ.[9] Addition of 5-fluorooxindole and KOH to the reaction mixture at this stage afforded the desired product **1**, which was isolated in 74% yield upon direct filtration of the reaction mixture (Scheme 4).



In conclusion, we have successfully developed an early amidation approach to 3-(4-amido)pyrrol-2-yl-2-indolinones. This approach relies on the installation of the amide side chain prior to pyrrole formation. We have demonstrated that the pyrrole could be assembled with the amide side chain in place via a hydrogenation reaction. The hydrogenation strategy helped avoid the scale-up and environmental issues typically associated with the use of zinc in the Knorr pyrrole synthesis reaction. This early amidation route circumvents the need to use activating agents and excess amine in the amide formation step.

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Experimental Section

***N*-[2-(Diethylamino)ethyl]-3-oxobutanamide 12.** Diketene (30.0 g; 357 mmol) was added to a 1000 mL three-neck round-bottom flask equipped with an addition funnel, N_2 inlet, and overhead stirrer. *tert*-Butyl methyl ether (500 mL) was transferred to the flask, and the solution was cooled to 0−5 °C using an ice−water bath. *N*,*N*-Diethylethylenediamine (33.3 g; 287 mmol) was added to the solution dropwise, maintaining the temperature below 5 °C. The ice−water bath was removed, and the solution was allowed to stir overnight at room temperature. Removal of the solvent in vacuo gave 53.1 g (265 mmol) of the product (93%), which was carried on to the next step without further purification.

***tert*-Butyl 4-[[[2-(diethylamino)ethyl]amino]carbonyl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate 14 via the Zinc Protocol.** *tert*-Butyl acetoacetate (60.0 g; 379 mmol) was added to a 1000 mL three-neck round-bottom flask equipped with a stopper, addition funnel, and temperature probe. Acetic acid (120 mL) was added to the flask and the mixture cooled to 5 °C. A solution of $NaNO_2$ (27.0 g; 391 mmol) in H_2O (60 mL) was added dropwise over 45 min to the three-neck flask, keeping the temperature below 10 °C. Upon completion of the addition, H_2O (45 mL) was added, and the solution was stirred for an additional 30 min and then allowed to stand at room temperature for 3 h. TLC (SiO_2; 30% ethyl acetate/hexanes) indicated complete consumption of starting material by this time. A pale yellow solution of oxime **3** was observed at this stage. The reaction was assumed to go to completion in quantitative yield (71.0 g; 379 mmol), and the solution was used directly in the next step.

Amide **12** (68.5 g; 342 mmol) was added to a 1000 mL three-neck round-bottomed flask along with acetic acid (175 mL). The resulting solution was heated to 65 °C, and Zn (1/8 quantity of 75.2 g; 1150 mmol) was added to the flask. Once at 65 °C, a solution of oxime **3** (1/8 quantity of 66.9 g; 357 mmol) was added. This process was continued until all the zinc and oxime were added. There was a 10−15 °C exotherm between additions; however, the reaction temperature was brought back to 65 °C before the next addition. After the last addition, the reaction mixture was heated to 75 °C and allowed to stir for 1 h. The reaction vessel was then cooled to room temperature, and the slurry was filtered through a coarse frit to remove the unreacted zinc. The filtrate was then transferred to a 2000 mL three-neck round-bottom flask equipped with an N_2 inlet and overhead stirrer. H_2O (300 mL) was added to the flask, and the solution was basified with 50% NaOH solution. Once the pH of the reaction solution reached 9.0, zinc salts started to form; excess NaOH was added until all zinc salts dissolved. The reaction mixture was then split into two batches, and each batch was extracted with CH_2Cl_2 (3 × 250 mL). The organic layers from both batches were combined and washed with brine (300 mL). The organics were concentrated and recrystallized from acetonitrile. The product, pyrrole **14**, was isolated as off-white crystals (60.6 g; 181 mmol; 53%). TLC conditions: 86:12:2 CH_2Cl_2/MeOH/NH_4OH; IR (NaBr) 3333, 3284, 3005, 1687, 1601, 1531, 1502, 1434, 1326, 1286 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1 H), 6.43 (s, 1 H), 3.45 (q, J = 5.4 Hz, 2 H), 2.62 (t, J = 5.9 Hz, 2 H), 2.55 (q, J = 7.0 Hz, 4 H), 2.47 (s, 3 H), 2.46 (s, 3 H), 1.55 (s, 9 H), 1.01 (t, J = 7.1 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 161.0, 134.5, 125.7,118.8, 118.3, 80.9, 51.5, 46.5, 36.7, 28.5, 13.4, 11.8, 11.7; HRMS (ES) found m/z 338.2447 ($M + H^+$), $C_{18}H_{31}N_3O_3$ + H requires 338.2443.

***tert*-Butyl 4-[[[2-(Diethylamino)ethyl]amino]carbonyl]-3,5-dimethyl-1*H*-pyrrole-2-carboxylate 14 via Hydrogenation.** *tert*-Butyl acetoacetate (30 g; 190 mmol) was added to three-neck round-bottom flask along with acetic acid (30 mL). The mixture was cooled to 0−3 °C under N_2, and a solution of $NaNO_2$ (18.3 g; 265 mmol) dissolved in H_2O (35 mL) was added dropwise maintaining the temperature below 10 °C. Once the addition was complete, the reaction solution was slowly warmed to room temperature. When the reaction was deemed complete by TLC (2 h), the mixture was partitioned between aqueous KCl solution (40 mL) and diethyl ether (50 mL). The aqueous layer was extracted further with diethyl ether (3 × 25 mL). The combined organics were washed with H_2O (3 × 35 mL), dried over Na_2SO_4, and concentrated in vacuo to afford oxime **3** as a pale yellow oil which was used in the next step without further purification.

Oxime **3** (20.0 g; 107 mmol) was added to a 500 mL Parr vessel along with 2.0 g of 5% dry Pd/C. Amide **12** (21.4 g; 107 mmol) was dissolved in acetic acid (220 mL) and charged to the Parr bottle. The vessel was purged with N_2 and H_2 and the mixture hydrogenated at 45 psig by heating at 65 °C for 7 h. After this time, the reaction mixture was cooled to room temperature and filtered to remove Pd, and the cake was washed with acetic acid. The filtrate was neutralized with 50% aqueous NaOH. CH_2Cl_2 (500 mL) was added, followed by more 50% aqueous NaOH until the pH of the aqueous phase was 13. The mixture was transferred to a separatory funnel, and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 350 mL), and the combined organics were washed with H_2O (2 × 250 mL). The washes were back-extracted with CH_2Cl_2 (250 mL), and the combined organics were concentrated in vacuo. The residue was dissolved in hot CH_3CN, and the resulting solution was filtered and cooled. The solids that formed were isolated by filtration to afford 27.7 g (83 mmol; 77%) of pyrrole **14**.

***N*-[2-(Diethylamino)ethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide 15.** Pyrrole **14** (20.0 g; 60 mmol) was added to a 2000 mL three-neck round-bottom flask equipped with an addition funnel, N_2 inlet, and overhead stirrer. A 3:1 mixture of 1 M H_2SO_4/MeOH and H_2O (1200 mL) was added dropwise (over 15 min) to the flask with stirring. Once the addition was complete, the solution was stirred at 65 °C for 3.5 h. The reaction mixture was cooled to 0−5 °C in an ice−water bath. H_2O (200 mL) was added, and the solution brought to a pH of 12−14 with 50% NaOH. Some salt formation was observed. The salts were easily filtered off, and the filtrate was transferred to a 2000 mL separatory funnel. The aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL). The organic phases were combined and washed with H_2O (3 × 300 mL) followed by a brine wash (300 mL). The organic phases were concentrated to dryness to yield **15** as a light brown oil (14.2 g; 60 mmol; quantitative yield) which was used in the next step without further purification: IR (NaBr) 3246, 2969, 1624, 1577, 1529, 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 6.44 (s, 1 H), 6.33 (s, 1 H) 3.45 (q, J = 5.8 Hz, 2 H), 2.62 (t, J = 6.1 Hz, 2 H), 2.56 (q, J = 7.1 Hz, 4 H), 2.46 (s, 3 H), 2.23 (s, 3 H), 1.01 (t, J = 7.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 132.6, 117.5, 114.3, 51.6, 46.5, 36.6, 13.5, 12.6, 11.7; HRMS (ES) found m/z 238.1919 ($M + H^+$), $C_{13}H_{23}N_3O$ + H requires 238.1921.

***N*-[2-(Diethylamino)ethyl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide 1.** Chloromethylenedimethylammonium chloride (7.8 g; 61 mmol) was added to a 1000 mL three-neck round-bottom flask equipped with an addition funnel, N_2 inlet, and overhead stirrer. Acetonitrile (84 mL) was added dropwise via the addition funnel to the flask. Compound **15** (13.7 g; 58 mmol) was dissolved in acetonitrile (116 mL) and added to the flask through the addition funnel. The amide chloride gradually dissolved and the reaction solution turned dark orange. After 15 min, an orange solid precipitated out of solution. The reaction was complete in 40 min. The 5-fluorooxindole (9.2 g; 61 mmol) and pulverized KOH (11.9 g; 213 mmol) were added to the reaction mixture, and stirring was continued. Acetonitrile (10 mL) was used to help transfer over reagents. An orange solid crashed out immediately. The reaction mixture was stirred at room temperature for 3.5 h, filtered, and dried to give **1** (16.9 g; 42 mmol) in 74% yield: IR (NaBr) 3298, 3230, 2968, 1676, 1627, 1590, 1544, 1498, 1334 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 9.4, 2.5 Hz, 1 H), 7.71 (s, 1 H), 7.43 (t, J = 5.6 Hz, 1 H), 6.92 (td, J = 9.1, 2.5 Hz, 1 H), 6.84 (dd, J = 8.5, 4.6 Hz, 1 H), 3.41−3.36 (m, 2 H), 2.65−2.58 (m, 6 H), 2.47 (s, 3 H), 2.43 (s, 3 H), 1.07 (t, J = 7.1 Hz, 6 H); HRMS (ES) found m/z 399.2204 ($M + H^+$), $C_{22}H_{27}FN_4O_2$ + H requires 399.2196.

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Supporting Information Available: ^1H and ^{13}C spectra of compounds **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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