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Short Note

2-Methyl-4-Oxo-4,5-Dihydro-1*H*-Pyrrole-3-Carboxylic Acid Phenylamide

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Abstract: 2-Methyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid phenylamide was obtained as a single product in an experiment on the cyclization modes of a glycine-derived enamino amide. High yield and operational simplicity are the main features of the presented synthetic procedure. Additionally, this result extends our previous observations on the cyclization reactions of similarly functionalized enamines, by revealing the preferred cyclization pathway under Boc-deprotection conditions.

Keywords: pyrrole-3-carboxylic acid; pyrrolin-4-one; β-enaminone; amide

1. Introduction

The synthesis of pyrrole-3-carboxylic acid amides is of significant interest because this substructure is central to remarkably successful drugs like Atorvastatin [1] and Sunitinib [2] (Figure 1).

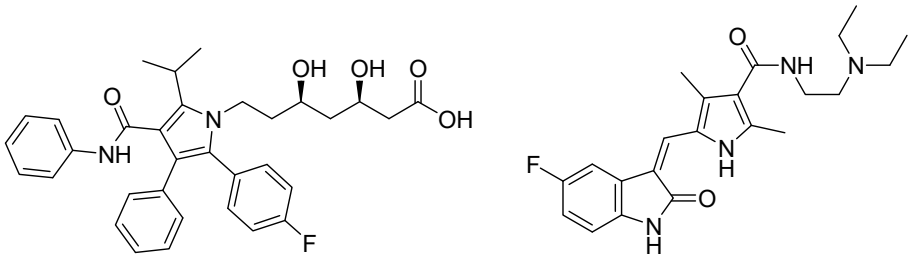

Figure 1. Structures of Atorvastatin and Sunitinib.

The structurally related 4-oxo derivatives of pyrrole-3-carboxylic acids, and the pyrrolin-4-ones in general, are also of interest as bioactive compounds with antimalarial [3] and HIV-1 protease inhibitory [4] activities, which has inspired the development of many approaches to their synthesis. In this regard, the cyclization of α-amino ynones [5–7] and the three-component reactions of 2,3-diketo esters, amines, and ketones [8] have shown significant scope. Another interesting approach is the ring-opening cyclization of cyclopropyl ketones with primary amines, which has been accomplished as a Ni(II)-catalyzed process [9] and also in an asymmetric variant, with the help of chiral Sc(III) complexes [10]. 1,3-Dicarbonyl compounds and their enamines have been widely used as precursors to pyrrolin-4-ones with carbamoyl, acyl, or alkoxycarbonyl substituent at the C3-position. A well-studied approach of this type is the oxidative cyclization of β-enaminones, involving a rearrangement step after the ring formation [11–14]. This oxidative cyclization has also been realized in a one-pot variant, starting from β-ketoamides [15]. Similar pyrrolinones have been synthesized by the Cu(II)-catalyzed cyclization of α-diazo-β-oxoamides with

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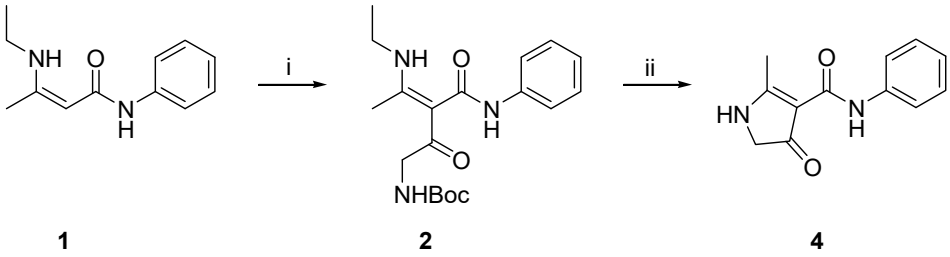
amines [16]. Iodine promoted cyclization of enaminone with aryl methyl ketones has also been demonstrated as a useful method for the synthesis of some pyrrolin-4-ones [17].

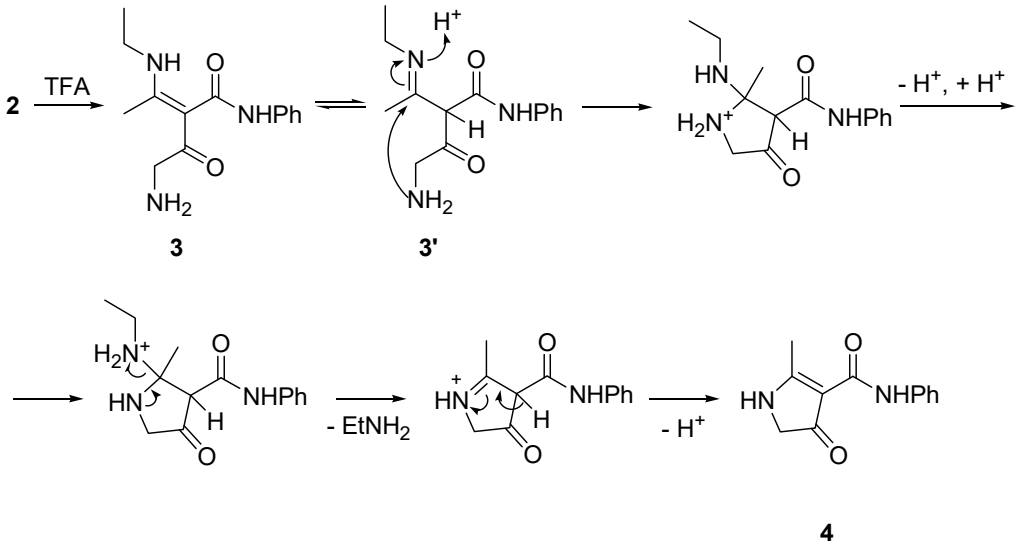
2. Results

In the course of our ongoing studies on a class of synthetic intermediates, obtained by the acylation of β-enamino amides with *N*-protected amino acids, we have observed two distinct modes of acid-catalyzed intramolecular cyclization in these compounds, leading to either enaminotetramic derivatives [18] or pyrrolin-4-ones [19]. Our experiments so far have focused on acid-stable protecting groups, which in both modes are retained in the final products, except for one unusual case of 2-nitrobenzoyl protection [20]. It was of interest to check whether an initial removal of the protecting group would change the cyclization mode. For this purpose, we turned our attention to acid-labile protection, such as Boc, and prepared compound **2** by the acylation of enaminoamide **1** with *N*-Boc-glycine (Scheme 1, i). The acylation was done using the mixed carbonic anhydride method [18,19] and gave the expected product **2** in an 87% yield. Compound **2** was then treated with TFA to remove the Boc protection from the glycine residue (Scheme 1, ii). Experiments were carried out with varying concentration of TFA in dichloromethane at room temperature and also in neat TFA. In all experiments, the pyrrolinone **4** was obtained as a single product in a 70–90% yield. The structure of **4** was determined on the basis of its ^{1}H and ^{13}C NMR spectra, which clearly indicate the retention of the phenyl amide moiety and departure of the ethylamino group from intermediate **2**. An interesting peculiarity that is observed in the ^{1}H and COSY NMR spectra of **4** is the long-range coupling between the exocyclic C2-methyl protons and the C5-methylene protons in the pyrrolinone ring (^{5}J = 1.8 Hz, see SI file 1). The formation of **4** is likely to proceed through the imino-tautomer **3′** of the unprotected intermediate, as a *5-exo-trig* addition followed by the elimination of ethylamine (Scheme 2). This mode of cyclization is different to the one observed in analogues of **2** with acid-stable *N*-protection, such as Troc or COOEt. The latter react only upon heating in neat TFA, with the *5-exo-trig* process taking place at the amide carbonyl, followed by the elimination of aniline [18]. Ethylenediamine analogues of **2**, on the other hand, follow the same mode of cyclization, but with retention of the acid-stable protecting groups [19].



Scheme 1. Synthesis of intermediate **2** and pyrrolinone **4**. Reagents and conditions: (i) $BocNHCH_2COOH$, NMM, EtOCOCl, CH_2Cl_2, 0 °C to r.t., 1h; (ii) TFA, r.t.

In conclusion, we have obtained 2-methyl-4-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid phenylamide (**4**) in a high yield, using an operationally simple protocol, not involving chromatographic purification of the product or any intermediate. This result suggests yet another approach to pyrrolin-4-one derivatives and complements our previously described synthesis of *N*-protected compounds of this type [19].



Scheme 2. Deprotection and cyclization of intermediate **2** with suggested *5-exo-trig* ring closure.

3. Materials and Methods

All reagents and solvents were purchased from Sigma-Aldrich, Darmstadt, Germany, and were used as supplied. Enamino amide **1** was obtained in a quantitative yield by the condensation of ethylamine and acetoacetanilide, following our published procedure [18,20]. NMR spectra were run on a Bruker NEO 400 (400/100 MHz $^{1}H/^{13}C$) spectrometer at BAS-IOCCP—Sofia. Chemical shifts (δ, ppm) are downfield from TMS. High-resolution mass spectral measurements were performed on a Waters Acquity—Synapt XS UPLC—mass spectrometry system. IR spectra were measured on a Bruker Alpha II FT IR spectrometer in KBr pellets. Melting point measurements were done in capillary tubes on a KRÜSS M5000 automatic mp meter and are not corrected.

*Synthesis of (4-Ethylamino-2-oxo-3-phenylcarbamoyl-pent-3-enyl)-carbamic acid tert-butyl ester (***2***):* To a magnetically stirred suspension of *N*-Boc-glycine (526 mg, 3 mmol) in CH_2Cl_2 (15 mL) was added *N*-methylmorpholine (3 mmol, 0.33 mL). The resulting solution was cooled in an ice bath and then ethyl chloroformate (3 mmol, 0.3 mL) was added. The mixture was left to stir for 5 min and after that a solution of enamino amide **1** (613 mg, 3 mmol) and DMAP (73 mg, 0.6 mmol) in CH_2Cl_2 (35 mL) was added in one portion. The ice bath was then removed, the reaction mixture was allowed to warm up to r.t. and was left to stir for one more hour. The reaction mixture was then transferred to a separatory funnel with 20 more mL of CH_2Cl_2 and was washed with aqueous (10:1) HCl. The aqueous layer was extracted with 20 more mL of CH_2Cl_2, the combined organic layers were dried with anhydrous sodium sulfate, the drying agent was removed by filtration and the solvent was distilled off. The crude α-C-acylated product **2** crystallized upon trituration with diethyl ether and was washed with small amount of the same solvent. Yield: 995 mg (92%), white solid, m.p. 156–157 °C; IR (cm^{-1}, KBr): 3434, 3255, 3225, 3122, 3051, 3005, 2983, 1707, 1637, 1598, 1581; ^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz): 1.19 (t, *J* = 7.2, 3H), 1.37 (s, 9H) 2.04 (s, 3H), 3.37 (m, 2H), 3.81 (d, 2H, *J* = 5.8), 6.61 (t, 1H, *J* = 5.8), 7.06 (m, 1H), 7.31 (m, 2H), 7.67 (d, 2H, *J* = 7.8), 10.14 (s, 1H), 11.37 (br s, 1H); ^{13}C-NMR (DMSO-d6, δ ppm): 15.5, 16.4, 28.7, 37.8, 46.5, 78.2, 106.7, 119.6, 123.7, 129.12, 140.0, 156.2, 163.8, 167.9, 189.1 (Only signals corresponding to the major tautomer are listed); HRMS *m*/*z* (ES+): calculated for $C_{19}H_{27}N_3NaO_4^+$ $[M+Na]^+$ 384.1894, found 384.1919; calculated for $C_{38}H_{54}N_6NaO_8+^+$ $[2M+Na]^+$ 745.3895, found 745.3906.

*Synthesis of 2-Methyl-4-oxo-4,5-dihydro-1H-pyrrole-3-carboxylic acid phenylamide (***4***):* To compound **2** (300 mg, 0.83 mmol), placed in a 100 mL round bottom flask with a magnetic stirrer bar, was added trifluoroacetic acid (10 mL) and the mixture was magnetically stirred for 10 min at room temperature. Then, water (50–60 mL) was poured into the flask and

the resulting suspension was left to stir for 30 min at room temperature. The obtained product was isolated by vacuum filtration on a sintered glass funnel and was rinsed consecutively with small amounts of water and diethyl ether. Alternatively, the product could be isolated by repetitive extractions in CH_2Cl_2, but the solubility in this solvent is poor. Yield: 162 mg (90%), white solid, m.p. 207 °C dec.; IR (cm^{-1}, KBr): 3185, 3082, 2952, 2924, 1674, 1593, 1541; ^{1}H-NMR (DMSO-d6, δ ppm, *J* Hz): 2.55 (dt, $^4J_{(H\text{-}C\text{-}C\text{-}N\text{-}H)}$ = 0.4, $^5J_{(H\text{-}C\text{-}C\text{-}N\text{-}C\text{-}H)}$ = 1.8, 3H, CH_3), 4.09 (dq, $^3J_{(H\text{-}C\text{-}N\text{-}H)}$ = 2.0, $^5J_{(H\text{-}C\text{-}N\text{-}C\text{-}C\text{-}H)}$ = 1.8, 2H, CH_2), 7.00 (m, 1H, Aryl CH, *para*), 7.29 (m, 2H, Aryl CH, *metha*), 7.58 (m, 2H, Aryl CH, *ortho*), 9.67 (br s, 1H, NH), 10.42 (s, 1H, CONH); ^{13}C-NMR (DMSO-d6, δ ppm): 17.1, 55.0, 103.7, 119.3, 122.9, 129.3, 139.7, 162.4, 181.2, 196.6; HRMS *m*/*z* (ES+): calculated for $C_{12}H_{12}N_2NaO_2^+$ $[M+Na]^+$ 239.0791, found 239.0782; calculatedd for $C_{12}H_{13}N_2O_2^+$ $[M+H]^+$ 217.0972, found 217.0968.

Supplementary Materials: S1.pdf—Processed NMR and mass spectra. S2-1.zip—Raw NMR data in Bruker-specific format and mol files. S2-2.zip—IR spectra.

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Data Availability Statement: The data presented in this study are available in this article and in the supporting Supplementary Materials.

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Conflicts of Interest: The authors declare no conflicts of interest.

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