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EFFICIENT PREPARATION OF UROCANIC ACID DERIVATIVES FROM HISTIDINE[1]

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Abstract – Urocanic acid derivatives have served as useful starting materials in several total synthesis endeavors in our lab. This paper describes a convenient, large-scale synthesis of several derivatives of urocanic acid via the net elimination of ammonia from histidine.

INTRODUCTION

Inspired by the structural complexity presented by several members of the oriodin alkaloids,[1] e.g. ageliferin (**3**),[2-4] we have initiated a number of total synthesis programs which feature the Diels-Alder reaction of 4-vinylimidazoles prominently.[5-9] The requisite 4-vinylimidazoles were prepared either from the corresponding 4-iodoimidazole derivative through a Stille cross-coupling reaction or from commercially available urocanic acid.[5, 7, 10] From time-to-time, we were unable to obtain urocanic acid from commercial sources, and as a result we have developed a method for its preparation (as the methyl ester) from histidine through a net elimination of ammonia.[11, 12] In this submission, we describe this chemistry along with the selective N-protection of the methyl ester.

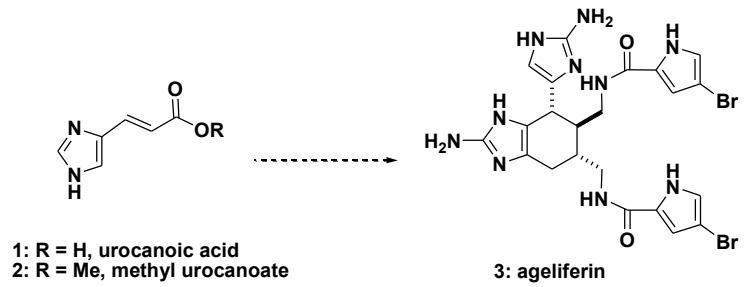
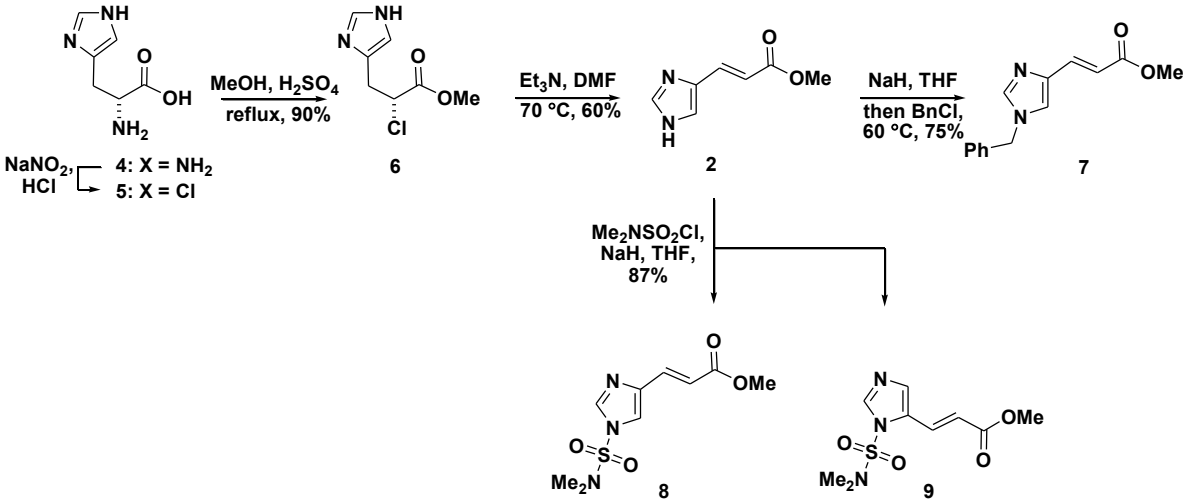


Figure 1. Urocanic acid and its relation to ageliferin

[1] This manuscript is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

RESULTS AND DISCUSSION

Although there are methods in the literature for the preparation of urocanic acid derivatives, these involve Wittig-like processes[13-17] or cross-coupling processes[18-21] which suffer from scalability or efficiency issues; therefore, we sought an alternative approach. Our attention was drawn immediately to histidine as it already contains the requisite carbon skeleton and just requires the introduction of unsaturation. A number of possibilities exist for effecting this transformation, but we elected to convert the amino group into a chloro group through diazotization in the presence of chloride ion, providing the α-chloro acid **5** in good yield.[22] This material was immediately converted to the methyl ester by a Fischer esterification to afford the α–chloro ester **6** (Scheme 1). After some experimentation it was found that heating a DMF solution of the ester and triethylamine at 70 °C for 48 h provided the methyl ester of urocanic acid **2** in 60% yield.



Scheme 1

In most of our total synthesis endeavors we have employed protected urocanoate esters specifically the benzyl- and dimethylsulfamoyl derivatives **8** and **9** respectively (Scheme 1). These can be prepared in a selective fashion by treatment of ester **2** with either BnCl or DMASCl under equilibrating conditions from which the least hindered nitrogen is protected.[7, 23] On larger scales, when we used the crude product directly from the elimination reaction, we found that if the reactions were not heated a second compound was produced in yields of up to 10%. X-Ray crystallography[24] of this derivative demonstrated that it was the regioisomeric product in which the DMAS group was attached to the more hindered nitrogen atom. We have found previously that with other protecting groups (e.g., PG = Bn, MOM, SEM) that mixtures of regioisomers are formed initially, but if the reaction mixture contains a small excess of the corresponding protecting group donor (BnCl, MOMCl, SEMCl) and is heated, isomerization occurs to provide predominantly the 4-isomer.[23]

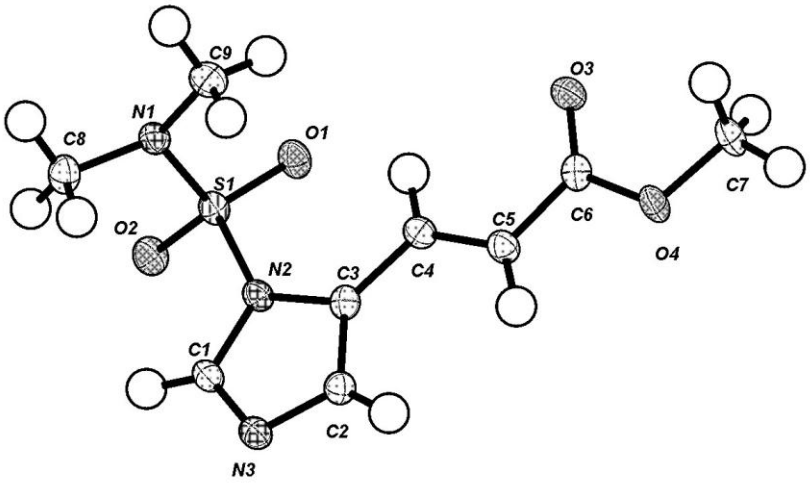


Figure 2. X-Ray crystal structure of the minor urocanoate ester **9**

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded as $CDCl_3$ solutions unless otherwise indicated.[25]

Methyl 3-(Imidazol-4(5)-yl)-2-chloropropanoate (6):[22] L-Histidine (10.0 g, 0.06 mol) was dissolved in conc. HCl (75 mL) and cooled in an ice-bath with stirring. $NaNO_2$ (10.0 g, 0.14 mol) in H_2O (20 mL) was added dropwise to the reaction mixture, maintaining the temperature between 0-5 °C. The mixture was stirred until the temperature reaches 0 °C, then for another 1-1.5 h at room temperature. The solution was filtered through a sintered-glass funnel to remove the precipitated NaCl, which was washed with MeOH and the filtrate was evaporated under vacuum. To the remaining thick yellow liquid MeOH was added and the NaCl ppt was also washed with MeOH. The combined MeOH solutions were evaporated under vacuum. The residual α-chloro urocanic acid was dissolved in anhydrous MeOH (150 mL), and then anhydrous Na_2SO_4 (2.0 g) and concentrated sulfuric acid (8 mL) was added. The solution was heated at reflux for 15 h. The MeOH was evaporated under vacuum and the resulting thick liquid was dissolved in a small quantity of water and neutralized with saturated aqueous $NaHCO_3$ solution until the evolution of CO_2 ceased. The cloudy aqueous layer was extracted repeatedly with CH_2Cl_2, the organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation to provide **6** as a thick yellow liquid (10.9 g, 90%) which was used directly in the next step without further purification.[22] ^{1}H NMR: δ 9.67 (b, 1H), 7.58 (s, 1H), 6.89 (s, 1H), 4.53 (t, J = 6.9 Hz, 3H), 3.70 (s, 3H), 3.30 (dd, J = 7.6, 14.5 Hz, 1H), 3.14 (dd, J = 7.6 Hz, 14.8 Hz, 1H). ^{13}C NMR: δ 170.1, 135.3, 133.2, 117.2, 56.1, 53.1, 33.3.

Methyl 3-(Imidazol-4(5)-yl)-2-propenoate (2): Ester **6** (10.0 g, 0.05 mol) was dissolved in anhydrous DMF (30 mL) and the reaction mixture was cooled to 0 °C, then Et_3N (20.8 mL, 0.15 mol, 3 equiv.) was

added slowly. The mixture was allowed to come to room temperature and then heated to 70 °C for 48 h. The mixture was cooled to room temperature and precipitated solids were filtered and washed with ethyl acetate. The ethyl acetate was removed under vacuum and the DMF was distilled off under vacuum. The resulting residue was purified by column chromatography (EtOAc) from which a white solid was obtained (4.84 g, 60%). Mp 92-94 °C.[26] ^{1}H NMR: δ 7.70 (s, 1H), 7.59 (d, *J* = 15.6 Hz, 1H), 7.28 (s, 1H), 6.45 (d, *J* = 15.6 Hz, 1H), 3.77 (s, 3H).

Methyl 3-(1-Benzylimidazol-4-yl)-2-propenoate (7): Ester **2** (20.0 g, 0.13 mol) was dissolved in THF (300 mL) under an N_2 atmosphere. The reaction mixture was cooled to 0 °C and NaH (6.3 g, 0.16 mol, 60% in mineral oil) was added portionwise. The reaction mixture was allowed to come to room temperature for 1.5 h, then again cooled to 0 °C and neat benzyl chloride (19.6 ml, 0.17 mol) was added dropwise. The resulting solution was stirred at 60 °C for 10 h. After quenching with water (5 ml), the solvent was removed under vacuum and the resulting solid was dissolved in CH_2Cl_2. The organic solution was separated and aqueous layer was extracted repeatedly with additional portions of CH_2Cl_2. The combined organic solutions were dried over anhydrous Na_2SO_4 and concentrated. The residue was triturated with hexane to provide the benzyl protected methyl ester (24.0 g, 75%) as a colorless solid which exhibited analytical data matching material prepared previously.[7]

Methyl 3-(1-(*N*,*N*-Dimethylsulfamoyl)imidazol-4-yl)-2-propenoate (8): Methyl ester **2** (20.0 g, 0.13 mol) was dissolved in THF (300 mL) under N_2 atmosphere. The reaction mixture was cooled to 0 °C and NaH (5.5 g, 0.14 mol, 60% in mineral oil) was added portionwise. The reaction mixture was allowed to come to room temperature for 1 h, then again cooled to 0 °C and neat *N*,*N*-dimethylsulfamoyl chloride (15.4 ml, 0.14 mol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred overnight. After quenching with water (5 ml), the solvent was removed under vacuum. The resulting solid was dissolved with CH_2Cl_2 and washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated. Finally it was triturated with hexane to obtain pure *N*,*N*-dimethylsulfamoyl protected methyl ester **8** (29.5 g, 87%) as colorless solid.[7] In some cases, the crude reaction mixture was purified by chromatography (CH_2Cl_2/ethyl acetate, 7:3→1:1) providing the **8** (30.0 g) and **9** (2.0 g) the latter as a colorless solid.

Methyl (2*E*)-3-(1-(*N*,*N*-Dimethylsulfamoyl)imidazol-5-yl)-2-propenoate (9): Mp: 150.5 °C. ^{1}H NMR ($CDCl_3$): δ = 7.99 (s, 1H), 7.87 (d, *J* = 16.0 Hz, 1H), 7.47 (s, 1H), 6.35 (d, *J* = 16.0 Hz, 1H), 3.78 (s, 3H), 2.87 (s, 6H); ^{13}C NMR ($CDCl_3$): δ = 166.5, 140.8, 131.9, 129.7, 128.5, 52.0, 38.2; FT-IR (KBr,

cm^{-1}): 3113, 2952, 1699, 1626, 1385, 1353, 1314, 1241, 1096. Anal. Calcd for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21. Found: C, 41.37; H, 4.98; N, 16.22.

X-Ray Crystallography:

Diffraction data were collected on a colorless prismatic crystal (approximate dimensions 0.35 x 0.15 x 0.05 mm^3) at low temperature (T = -173 °C) on a Bruker SMART APEX CCD diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The cell parameters for the organic complex were obtained from the least-squares refinement of the spots (from 60 collected frames) using the SMART program. A hemisphere of the crystal data was collected up to a resolution of 0.75 Å, and the intensity data were processed using the Saint Plus program. All calculations for structure determination were carried out using the SHELXTL package (version 6.1).[24] Initial atomic positions were located by direct methods using XS, and the structure was refined by least-squares methods using SHELX with 2615 independent reflections and within the range of Θ = 1.98-28.27 (completeness 92.7%). Calculated hydrogen positions were input and refined in a riding manner along with the attached carbons. CCDC 746411 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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