# A Stereospecific Route to (*Z*)-Urocanic Acids

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**Abstract:** (*Z*)-Urocanic acid and its derivatives can be made stereospecifically by ring-opening of pyrrolo[1,2-*c*]imidazol-5-ones in aqueous tetrahydrofuran.

**Key words:** gas-phase reactions, hydrolyses, heterocycles, lactams, urocanic acids

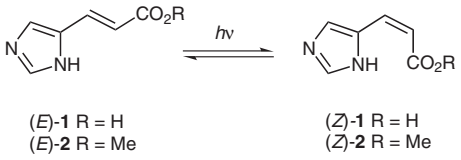
(*E*)-Urocanic acid [(*E*)-**1**] is a major chemical component of the epidermis, formed from histidine by the enzyme histidase in the *stratum corneum*.[1] Upon ultraviolet irradiation of the skin, *trans*-urocanic acid [(*E*)-**1**] isomerizes to the *cis*-form (*Z*)-**1**, which is of current biomedical[2] and photophysical[3] interest (Scheme 1). In particular, (*Z*)-urocanic acid [(*Z*)-**1**] is known to have an immunosuppressive effect in vivo or in vitro and its mode of action has been recently investigated.[4]

Photoisomerization of the commercially available *E*-isomer (*E*)-**1**[5] or its methyl ester (*E*)-**2**[6] are the only known routes to *Z*-urocanic acid [(*Z*)-**1**]. A photostationary equilibrium between the two isomers is attained (at which the conversion reaches 70%) and so a chromatographic separation is necessary.[5,7]

Relatively few derivatives of urocanic acids have been synthesized, especially as *Z*-isomers, though fluorinated analogues provide an interesting exception.[8]

In this paper, we report a new, stereospecific route to (*Z*)-urocanic acid [(*Z*)-**1**] and its derivatives, by ring-opening of the pyrrolo[1,2-*c*]imidazol-5-one (azapyrrolizinone[9–12]) system **4**. These heterocycles are best made by flash vacuum pyrolysis (FVP) of (imidazol-4-yl)acrylate esters **2**, by an isomerization-elimination-electrocyclization sequence[10] or by FVP of 2-substituted (imidazol-1-yl)acrylate esters **3**, in which directed sigmatropic migration of the 1-substituent precedes the elimination and cyclization steps (Scheme 2).[11,12]

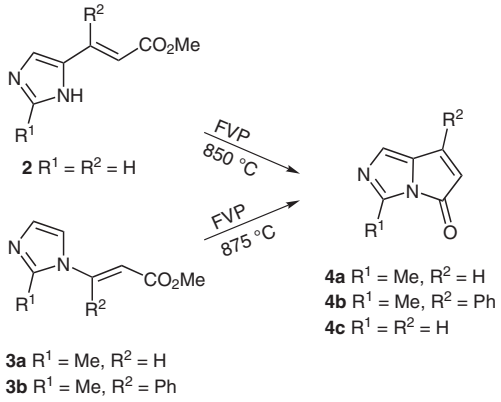
Few reactions of azapyrrolizinones have been published. However, pyrrolizin-3-ones themselves are readily ring-opened by treatment with hard nucleophiles[7,13] and the aza-analogues, which have an imidazole unit as a formal leaving group, would be expected to show greater reactivity.




(*E*)-**1** R = H
(*E*)-**2** R = Me

(*Z*)-**1** R = H
(*Z*)-**2** R = Me

**Scheme 1**




**2** $R^1 = R^2 = H$

**4a** $R^1$ = Me, $R^2$ = H
**4b** $R^1$ = Me, $R^2$ = Ph
**4c** $R^1 = R^2 = H$

**3a** $R^1$ = Me, $R^2$ = H
**3b** $R^1$ = Me, $R^2$ = Ph

**Scheme 2**

In practice, heating **4a**–**c** in aqueous THF (in the absence of any acidic or basic reagents) for three hours provided (*Z*)-urocanic acid [(*Z*)-**1**] and its analogues (*Z*)-**5a**,**b** in high yields (Scheme 3). The progress of the reaction could be monitored by the disappearance of the characteristic yellow color of the azapyrrolizinones. For the preparation of (*Z*)-**1**, it is particularly important to minimize decomposition of the azapyrrolizinone **4c** by adding the THF–water mixture directly to the azapyrrolizinone in the FVP cold finger trap and carrying out the hydrolysis immediately after the pyrolysis step. Isolation and manipulation of the azapyrrolizinone **4c** can cause decomposition.

After the hydrolysis step, the products were isolated simply by removal of the solvents without the need for chromatography. In this way, the *Z*-urocanic acid [(*Z*)-**1**] and its derivatives (*Z*)-**5a**,**b** were obtained in 72–89% overall yields based on the pyrolysis precursor. The *Z*-configuration of the alkene unit of (*Z*)-**1** and (*Z*)-**5a** was clear from their NMR spectra ($^3J$ = 12.5–13.0 Hz) and in the case of (*Z*)-**5b** by a NOESY experiment. No isomerization of the alkene took place under the hydrolysis conditions.

Good temperature control of the FVP step is essential. Thus, on one occasion during optimization of the route to (*Z*)-**1**, 4-ethynylimidazole (**7**) (15%) was obtained as an impurity, which could be separated by chromatography after the hydrolysis. Its $^1$H-coupled $^{13}$C NMR spectrum

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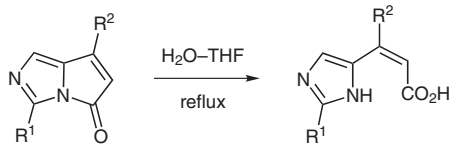
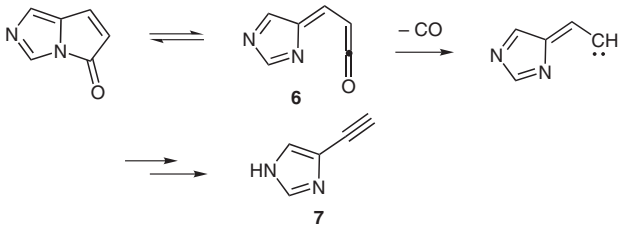



**4a** $R^1$ = Me, $R^2$ = H
**4b** $R^1$ = Me, $R^2$ = Ph
**4c** $R^1$ = $R^2$ = H

(*Z*)-**5a** $R^1$ = Me, $R^2$ = H
(*Z*)-**5b** $R^1$ = Me, $R^2$ = Ph
(*Z*)-**1** $R^1$ = $R^2$ = H

**Scheme 3**




**Scheme 4**

confirmed the presence of the ethynyl group ($^1J_{C,H}$ = 251.9 Hz). This compound has been reported experimentally only in the patent literature. The mechanism of its formation probably involves decarbonylation of the ring-opened ketene **6** and rearrangement of the resulting carbene (Scheme 4). Further elution of the column afforded (*Z*)-urocanic acid [(*Z*)-**1**] (46%).

In conclusion, we have described optimized conditions for the stereospecific synthesis of *Z*-urocanic acid [(*Z*)-**1**] and its analogues, substituted in either the imidazole ring, or in the ring and in the alkene side-chain. The route involves the formation and controlled hydrolysis of 'dehydrourocanic acids', the pyrrolo[1,2-*c*]imidazol-5-ones **4**.

$^1$H and $^{13}$C NMR spectra were recorded at 250 (or 200) MHz and 63 (or 50) MHz, respectively. Chemical shifts are given in ppm relative to TMS. Mass spectra were recorded under electron impact conditions.

Flash Vacuum pyrolysis (FVP) reactions were carried out by distillation of the substrate in vacuo through an electrically heated silica furnace tube (35 × 2.5 cm). Unless stated otherwise, products were trapped in a U-tube situated at the exit point of the furnace and cooled with liquid $N_2$. Pyrolysis conditions are quoted as follows: substrate, quantity, furnace temperature ($T_f$), inlet temperature ($T_i$), pressure range (*P*), pyrolysis time (*t*), and products.

**(*Z*)-3-(2-Methyl-3*H*-imidazol-4-yl)acrylic Acid [(*Z*)-5a]**

FVP of methyl 3-(2-methylimidazol-1-yl)acrylate (**3a**; 105 mg) (conditions: $T_f$ 875 °C, $T_i$ 120 °C, *P* 0.020–0.065 Torr, *t* 15 min) gave a solid yellow pyrolysate of 3-methylpyrrolo[1,2-*c*]imidazol-5-one (**4a**).[12] The entire crude pyrolysate was dissolved in a mixture of THF (2 mL) and $H_2O$ (10 mL), then transferred to a round-bottomed flask and heated under reflux for 3 h during which time decolorization occurred. THF and $H_2O$ were removed using a rotary evaporator and the product was dried under vacuum (oil pump) for 4 h to afford (*Z*)-**5a**; yield: 85 mg (89% for the two steps);[7,14] mp >190 °C (dec. with gas evolution).

$^1$H NMR (DMSO-$d_6$): δ = 7.52 (1 H, s), 6.81 (1 H, d, $^3J$ = 12.8 Hz), 5.62 (1 H, d, $^3J$ = 12.8 Hz), 2.39 (3 H, s).

$^{13}$C NMR (DMSO-$d_6$): δ = 167.24 (q), 144.95 (q), 133.90 (q), 129.98, 122.21, 118.31, 13.27.

MS: *m*/*z* (%) = 152 ($M^+$, 90), 135 (81), 134 (77), 108 (61), 107 (97), 106 (100), 105 (62), 79 (67).

HRMS: *m*/*z* calcd for $C_7H_8N_2O_2$ ($M^+$): 152.0586; found: 152.0587.

**(*Z*)-3-(2-Methyl-3*H*-imidazol-4-yl)-3-phenylacrylic Acid [(*Z*)-5b]**

FVP of methyl 3-(2-methylimidazol-1-yl)-3-phenylacrylate (**3b**; 105 mg) (conditions: $T_f$ 875 °C, $T_i$ 160 °C, *P* 0.010–0.060 Torr, *t* 15 min) gave solid yellow 3-methyl-7-phenylpyrrolo[1,2-*c*]imidazol-5-one (**4b**).[12] The entire crude pyrolysate was dissolved in a mixture of THF (2 mL) and $H_2O$ (10 mL), then transferred to a round-bottomed flask and heated under reflux for 6 h during which time decolorization occurred. THF and $H_2O$ were removed using a rotary evaporator and the product was dried under vacuum (oil pump) for 4 h to afford (*Z*)-**5b**; yield: 71 mg (72% for the two steps); mp >170 °C (dec. with gas evolution).

$^1$H NMR (DMSO-$d_6$): δ = 7.70–7.62 (5 H, br m), 7.14 (1 H, s), 5.85 (1 H, s), 2.68 (3 H, s).

$^{13}$C NMR (DMSO-$d_6$): δ = 167.48 (q), 145.66 (q), 143.51 (q), 141.34 (q), 136.05 (q), 129.57, 129.33 (2 CH), 129.15 (2 CH), 122.57, 121.26, 13.88.

MS: *m*/*z* (%) = 228 ($M^+$, 42), 210 (27), 183 (70), 182 (100), 181 (72), 169 (57), 168 (60), 128 (63), 115 (63), 114 (61).

HRMS: *m*/*z* calcd for $C_{13}H_{12}N_2O_2$ ($M^+$): 228.0898; found: 228.0895.

**(*Z*)-3-(3*H*-Imidazol-4-yl)acrylic Acid [*cis*-Urocanic Acid, (*Z*)-1]**

Due to the instability of pyrrolo[1,2-*c*]imidazol-5-one (**4c**) in air, which led to the formation of insoluble material, a preparative pyrolysis[10] of methyl (*E*)-3-(3*H*-imidazol-4-yl)acrylate[15] [methyl (*E*)-urocanate] [(*E*)-**2**; 312 mg, 20 mmol] (conditions: $T_f$ 850 °C, $T_i$ 220 °C, *P* 0.010–0.060 Torr, *t* 20 min) was performed using a cold-finger trap (cooled by a mixture of dry-ice and acetone) to collect the product (cf. ref. 10). The connection between the furnace tube and the cold-finger was wrapped in aluminum foil, allowing the product to condense almost exclusively on the cold surface of the trap. The solid yellow pyrrolo[1,2-*c*]imidazol-5-one (**4c**) obtained, was frozen into a mixture of THF (2 mL) and $H_2O$ (10 mL) to minimize degradation of **4c**. The cold finger was allowed to warm to r.t. under $N_2$, then the yellow solution of **4c** in THF–$H_2O$ was transferred to a round-bottomed flask and heated under reflux for 45 min during which time the color faded. The solvent was removed using a rotary evaporator then dried at the oil pump for 3 h to afford (*Z*)-**1** as an off-white solid; yield: 220 mg (78%); mp 169–171 °C (Lit.[16] mp 171–173 °C).

$^1$H NMR (DMSO-$d_6$): δ = 8.16 (1 H, s), 7.67 (1 H, d, *J* = 0.9 Hz), 6.88 (1 H, d, $^3J$ = 12.9 Hz), 5.68 (1 H, d, $^3J$ = 12.9 Hz).

$^{13}$C NMR (DMSO-$d_6$): δ = 167.26 (q), 136.02, 133.91 (q), 129.90, 123.32, 118.66.

**4-Ethynylimidazole (7)**

In an early reaction carried out under nonoptimized conditions, FVP of methyl (*E*)-3-(3*H*-imidazol-4-yl)acrylate [(*E*)-**2**; 518 mg, 3.4 mmol] (conditions: $T_f$ >850 °C, $T_i$ 180–220 °C, *P* 0.01–0.1 Torr, *t* 30 min] was carried out as above. Under $N_2$, the trap was rinsed with acetone (ca. 50 mL). The solution was poured into a round-bottomed flask and the acetone was removed at the oil pump, keeping the temperature of the solution below 0 °C. THF (8 mL) and $H_2O$ (45 mL) were added and the mixture was heated at reflux for 3 h. The solvents were removed using a rotary evaporator successively under water pump and oil pump pressure. Dry flash chromatography on silica gel using pure EtOAc as eluent afforded 4-ethy-

nylimidazole (**7**) as white crystals; yield: 47 mg (15%). This compound has been claimed in a patent,[17] but our $^1$H NMR spectrum is not in agreement with the reported data; mp 100.5–101 °C (hexane–EtOAc).

$^1$H NMR (acetone-$d_6$): δ = 10.05 (1 H, br), 7.74 (1 H, d, $^4J$ = 1.1 Hz), 7.42 (1 H, d, $^4J$ = 1.1 Hz), 3.58 (1 H, s).

$^{13}$C NMR (acetone-$d_6$): δ = 134.95, 122.99, 119.35 (q), 77.49, 76.28 (one quaternary signal not assigned).

MS: *m*/*z* (%) = 92 ($M^+$, 100), 65 (32), 41 (43), 38 (40).

HRMS: *m*/*z* calcd for $C_5H_4N_2$ ($M^+$): 92.0374; found: 92.0375.

Further elution with a mixture of EtOAc–MeOH (4:1) yielded (*Z*)-urocanic acid [(*Z*)-**1**]; yield: 217 mg (46%); mp 164–166 °C (dec.) (EtOH–EtOAc) (Lit.[16] mp 171–173 °C).

The spectroscopic data were identical with those reported above.

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