Some Transformations of Alkyl Heteroarylpyruvates

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The design of novel synthetic routes for unsaturated amino acids has received much attention in the last decade.[1] We have previously reported on various syntheses of heterocyclic amino acids which could be converted into several heterocyclic systems.[2] We now wish to demonstrate that alkyl heteroarylpyruvates, for which we have recently developed an efficient synthesis and which exist exclusively in the enol form,[3] are excellent synthons for heterocyclic dehydroamino acids of structure **2** (R = Et). Thus, the substrates **1** (R = Et) are transformed in the presence of a boiling ethanolic solution of ammonium formate into the unsaturated esters **2** (R = Et) (Scheme 1).

The X-ray analyses of **2a** and **2c** show the *Z* configuration around the C_2C_3 double bond (Figure 1). The amino group in these compounds resisted most attempted acylations; an exception was benzoylation in the presence of pyridine to give **3**.[4] Reaction of **2** (R = Et) with *N*,*N*-dimethylformamide dimethyl acetal in boiling toluene afforded the 2-((((dimethylamino)methylene)amino)propenoates **4**. Compound **4a** reacted with hydrazine to give dihydro-1,2,4-triazin-6-one derivative **5a**. We had prepared related derivatives of this heterocyclic system previously, starting from natural amino acids.[5] Although we have no unambiguous proof for the structure of **5a** as given, spectroscopic data favor the 4,5-dihydro formula. In this connection, it should be mentioned that dihydro-1,2,4-triazin-6-ones, obtained from azirine-3-carboxamides and hydrazine, were assigned on the basis of spectroscopic data to be 4,5-dihydro derivatives.[6]

In addition to the amination of esters **1** (R = Et) to give **2** (R = Et), the free hydroxy acid **1a** (R = H) could also be converted with ammonium formate into **2a** (R = H). All attempts to convert the esters or acids **1** into **2** in the presence of other amination reagents have failed so far.[7] The hydroxy ester **1a** (R = Et) upon bromination reacted with thiourea in the presence of *N*-methylmorpholine to give the thiazole **6a**.[9] This is another example of the formation of heterocyclic systems where two different heterocyclic rings are linked directly through carbon–carbon bonds.[2a,b,11]

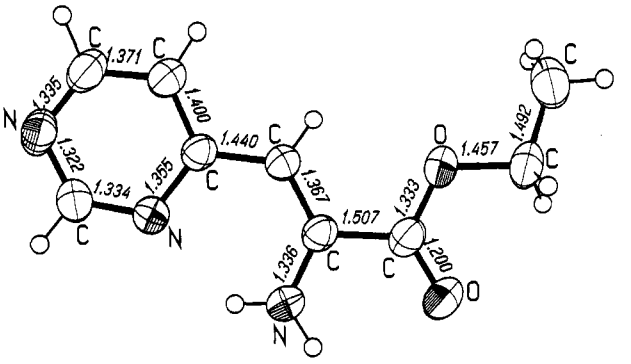
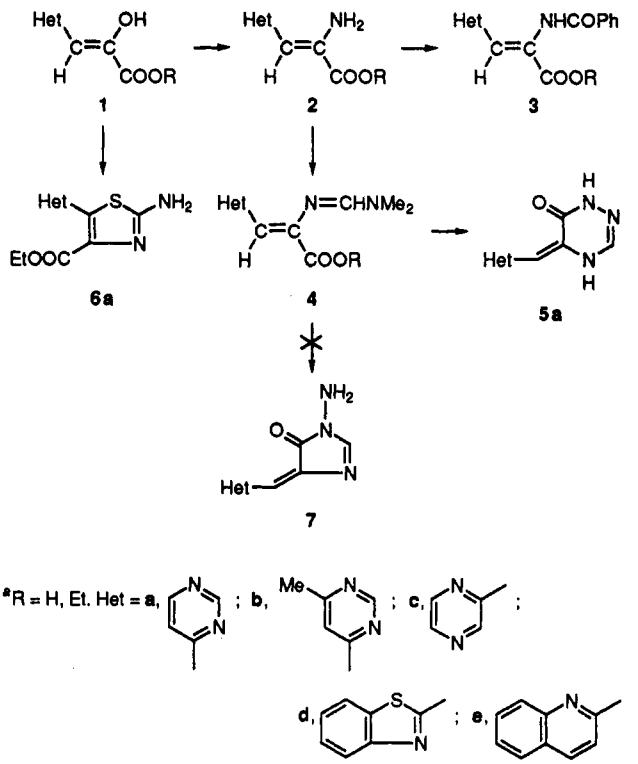


Figure 1. ORTEP view of pyrimidine derivative **2a**.

Scheme 1[a]



Experimental Section

General Methods. Melting points are not corrected. ^{1}H NMR spectra were taken on a Varian EM 360 L spectrometer and mass spectra were taken on a VG Analytical spectrometer Autospec Q either with electron ionization at 70 eV or FAB. Elemental analyses were performed on a Perkin-Elmer CHN Analyzer 2400, and for TLC analyses TLC Kieselgel with 254-nm fluorescent indicator on aluminum cards, thickness 0.2 mm, was used.

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(1) (a) Schmidt, U.; Liebknecht, A.; Wild, J. *Synthesis* **1988**, 159. (b) Cativela, C.; Diaz de Villegas, M. D.; Mayoral, J. A.; Avenoza, A.; Roy, M. A. *J. Heterocycl. Chem.* **1988**, *25*, 851.

(2) (a) Kolar, P.; Petrič, A.; Tišler, M.; Felluga, F. *J. Heterocycl. Chem.* **1991**, *28*, 1715. (b) Kolar, P.; Tišler, M. *Z. Naturforsch.* **1991**, *46b*, 1110. (c) Dobnikar, M.; Kočevar, M.; Polanc, S.; Tišler, M.; Verček, B. *Heterocycles* **1989**, *29*, 281. (d) Zupet, R.; Tišler, M.; Golič, L. *J. Heterocycl. Chem.* **1991**, *28*, 1731.

(3) Zupet, R.; Tišler, M. *Synth. Commun.* **1992**, *22*, 2245.

(4) The following acylation reagents have been used without success: acetyl chloride and pyridine, benzyl chloroformate and pyridine, acetic anhydride and pyridine (all reactions were conducted under reflux) or benzoyl chloride in the presence of 4-(dimethylamino)pyridine. When di-*tert*-butyl dicarbonate was used, after heating only transesterification occurred, and **2a** was thus converted to the corresponding *tert*-butyl ester.

(5) Smodiš, J.; Zupet, R.; Petrič, A.; Stanovnik, B.; Tišler, M. *Heterocycles* **1990**, *30*, 393.

(6) (a) Nishiwaki, T.; Saito, T. *J. Chem. Soc. C* **1971**, 2648. (b) Nishiwaki, T.; Saito, T. *Chem. Commun.* **1970**, 1479.

(7) Although literature reports on some transformations of pyruvates with aromatic amines,[8] our experiments with various amines and ammonia and its salts were unsuccessful. For example, alkyl heteroarylpyruvates did not react with aniline under the same reaction conditions as with ammonium formate; transformations did not occur with *p*-toluidine or its hydrochloride, ethyl 4-aminobenzoate, or benzylamine either under neutral conditions or in the presence of formic, acetic, hydrochloric, or *p*-toluenesulfonic acid. No transformation was observed either with ammonium chloride or acetate, whereas with aqueous or ethanolic ammonia, the corresponding amides of heteroarylpyruvates were formed.

(8) (a) Chong, R. J.; Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1986**, *27*, 5323. (b) Butenandt, A.; Bickert, E.; Däuble, M.; Köhrman, K. *Chem. Ber.* **1959**, *92*, 2172.

(9) 2-Amino-4-(ethoxycarbonyl)thiazole was obtained similarly from ethyl bromopyruvate and thiourea.[10]

(10) Erlenmayer, H.; Morel, C. J. *Helv. Chim. Acta* **1942**, *25*, 1073.

(11) Unpublished results from this laboratory.

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General Procedure for the Preparation of Ethyl 2-Amino-3-heteroarylpropenoates. The corresponding ethyl 2-hydroxy-3-heteroarylpropenoate (5–20 mmol) was treated with a double molar quantity of ammonium formate and the ethanolic solution (100 mL) was heated for 2 h. The progression of the reaction was monitored by TLC ($CHCl_3$:MeOH = 10:1 as solvent). After the solvent was removed at reduced pressure, ice-cold water (50 mL) was added and the crystalline product was filtered. In this manner the following compounds were prepared.

Ethyl 2-amino-3-(4-pyrimidinyl)propenoate (2a, R = Et): mp 80.5–81.5 °C (*from n-heptane*), *in* 82% yield. ^1H NMR ($CDCl_3$): δ 1.30 (3H, t, CH_2Me), 4.30 (2H, q, CH_2Me), 6.00 (1H, s, —CH=), 7.30 (1H, dd, H_5), 8.55 (1H, d, H_6), 7.50–8.10 (2H, br s, NH_2), 9.15 (1H, d, H_2); $J_{5,6}$ = 6.0, $J_{2,5}$ = 1.0, J_{Et} = 7.5 Hz. Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.09; H, 5.55; N, 21.88.

Ethyl 2-amino-3-(6-methyl-4-pyrimidinyl)propenoate (2b, R = Et): mp 119.5–121.5 °C (from di-*n*-propyl ether), in 78% yield. ^1H NMR ($CDCl_3$): δ 1.40 (3H, t, CH_2Me), 2.45 (3H, s, Me), 4.35 (2H, q, CH_2Me), 5.95 (1H, s, —CH=), 7.25 (1H, s, H_5), 7.50–8.00 (2H, br s, NH_2), 9.00 (1H, s, H_2); J_{Et} = 8.0 Hz. Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.70; H, 6.20; N, 20.33.

Ethyl 2-amino-3-(2-pyrazinyl)propenoate (2c, R = Et): mp 109–111 °C (from *n*-heptane), in 85% yield. ^1H NMR ($CDCl_3$): δ 1.40 (3H, t, CH_2Me), 4.45 (2H, q, CH_2Me), 6.30 (1H, s, —CH=), 6.40–7.35 (2H, br s, NH_2), 8.25 (1H, d, H_5), 8.55 (1H, d, H_6), 8.60 (1H, s, H_3), $J_{5,6}$ = 1.0, J_{Et} = 8.0 Hz. Mass spectrum (FAB) *m/z* (rel intensity): 194 (MH^+, 0.86), 105 (1.0). Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.40; H, 5.40; N, 21.66.

Ethyl 2-amino-3-(2-benzothiazolyl)propenoate (2d, R = Et): mp 122–123.5 °C (from a mixture of ethyl acetate and di-*n*-propyl ether), *in* 71% yield. ^1H NMR ($CDCl_3$): δ 1.40 (3H, t, CH_2Me), 4.40 (2H, q, CH_2Me), 6.35 (1H, s, —CH=), 6.80–7.35 (2H, br s, NH_2), 7.35–7.60 (2H, m, H_5H_6), 7.70–8.15 (2H, m, H_4H_7); J_{Et} = 7.5 Hz. Anal. Calcd for $C_{12}H_{12}N_2O_2S$: C, 58.04; H, 4.87; N, 11.28. Found: C, 58.31; H, 4.97; N, 10.79.

Ethyl 2-amino-3-(2-quinolyl)propenoate (2e, R = Et): mp 94.5–95.5 °C (from *n*-heptane), in 85% yield. ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, CH_2Me), 4.40 (2H, q, CH_2Me), 6.30 (1H, s, —CH=), 7.15–7.45 (2H, br s, NH_2), 7.25 (1H, d, H_3), 7.20–7.75 (4H, m, $H_5H_6H_7H_8$), 8.05 (1H, d, H_4); $J_{3,4}$ = 9.0, J_{Et} = 7.5 Hz. Exact mass calcd for $C_{14}H_{14}N_2O_2$: *m/z* 242.1055, found *m/z* 242.1056.

Ethyl 2-(Benzoylamino)-3-(4-pyrimidinyl)propenoate (3a, R = Et). A solution of compound **2a** (R = Et) (10 mmol) in dichloromethane (100 mL) was treated with pyridine (2 mL), and under stirring benzoyl chloride (10 mmol) was added dropwise. After addition was complete the reaction mixture was stirred at room temperature for 2 h and extracted with water (twice with 5 mL). The organic layer was dried with anhydrous sodium sulfate, the solvent was removed at reduced pressure, and the solid residue was crystallized from *n*-heptane: yield 60%; mp 87–89 °C. ^1H NMR ($CDCl_3$): δ 1.45 (3H, t, CH_2Me), 4.45 (2H, q, CH_2Me), 6.20 (1H, s, —CH=), 7.25 (1H, dd, H_5), 7.50–7.80 (3H, m, $H_{3'}H_{4'}H_{5'}$), 8.00–8.30 (2H, m, $H_{2'}H_{6'}$), 8.85 (1H, d, H_6), 9.45 (1H, d, H_2), 12.90 (1H, s, NH); $J_{5,6}$ = 5.0, $J_{2,5}$ = 1.0, J_{Et} = 7.5 Hz. Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.60; H, 4.93; N, 14.06.

Ethyl 2-(Benzoylamino)-3-(2-pyrazinyl)propenoate (3c, R = Et) was prepared similarly, mp 119–119.5 °C (from *n*-heptane) in 86% yield. ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, CH_2Me), 4.45 (2H, q, CH_2Me), 6.40 (1H, s, —CH=), 7.45–7.80 (2H, m, $H_{3'}H_{4'}H_{5'}$), 7.90–8.20 (2H, m, $H_{2'}H_{6'}$), 8.50 (1H, d, H_3), 8.65 (1H, dd, H_6), 8.70 (1H, d, H_5), 12.40 (1H, s, NH); $J_{3,6}$ = 1.0, $J_{4,6}$ = 1.5, J_{Et} = 7.0 Hz. Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.94; H, 4.74; N, 14.43.

2-(Benzoylamino)-3-(4-pyrimidinyl)propenoic acid (3a, R = H). The above ester (5 mmol) and aqueous NaOH (15 mL of 1 N) were heated under reflux for 2 min. The hot reaction mixture was acidified with hydrochloric acid to pH = 2–3. Upon cooling, the product was filtered and crystallized from *n*-propanol, mp 221–222 °C dec (92% yield). ^1H NMR (DMSO-d_6): δ 7.60 (1H, s, —CH=), 7.65 (1H, dd, H_5), 7.60–7.95 (3H, m, $H_{3'}H_{4'}H_{5'}$), 7.95–8.25 (2H, m, $H_{2'}H_{6'}$), 8.90 (1H, d, H_6), 9.35 (1H, d, H_2), 12.25 (1H, s, NH); $J_{5,6}$ = 5.0, $J_{2,5}$ = 1.0 Hz. Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.19; H, 3.95; N, 15.85.

2-(Benzoylamino)-3-(2-pyrazinyl)propenoic acid (3c, R=H) was prepared similarly in 95% yield, mp 164.5–166 °C dec (from water). ^1H NMR (DMSO-d_6): δ 6.85 (1H, s, —CH=), 7.50–7.90 (3H, m, $H_{3'}H_{4'}H_{5'}$), 8.55 (1H, d, H_3), 8.80 (1H, dd, H_6), 7.90–8.25 (2H, m, $H_{2'}H_{6'}$), 8.95 (1H, d, H_5), 12.80 (1H, s, NH); $J_{3,6}$ = 3.0, $J_{5,6}$ = 1.0 Hz. Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.78; H, 3.89; N, 15.42.

Ethyl 2-(((Dimethylamino)methylene)amino)-3-(4-pyrimidinyl)propenoate (4a). The amino acid **2a** (R = Et) (10 mmol) was dissolved in dry toluene (50 mL), *N,N*-dimethylformamide dimethyl acetal (1.5 mL) was added, and the reaction mixture was heated under reflux for 1 h. The solvent was evaporated and the residue was crystallized from *n*-heptane, mp 67–68 °C (80% yield). ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, CH_2Me), 3.15 (6H, s, NMe_2), 4.25 (2H, q, CH_2Me), 6.80 (1H, s, —CH=), 8.15 (1H, s, $CHNMe_2$), 8.50 (1H, dd, H_5), 8.65 (1H, d, H_6), 9.20 (1H, d, H_2); $J_{5,6}$ = 4.0, $J_{2,5}$ = 1.0, J_{Et} = 8.0 Hz. Anal. Calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.09; H, 6.35; N, 22.38.

Ethyl 2-(((Dimethylamino)methylene)amino)-3-(2-pyrazinyl)propenoate (4c) was obtained in a similar way in 88% yield, mp 95–96.5 °C (from *n*-hexane). ^1H NMR ($CDCl_3$): δ 1.35 (3H, t, CH_2Me), 3.15 (6H, s, NMe_2), 4.30 (2H, q, CH_2Me), 6.95 (1H, s, —CH=), 8.05 (1H, s, $CHNMe_2$), 8.35 (1H, d, H_6), 8.55 (1H, dd, H_5), 9.85 (1H, d, H_3); $J_{5,6}$ = 2.0, $J_{3,6}$ = 1.0, J_{Et} = 8.0 Hz. Anal. Calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.45; H, 6.43; N, 22.75.

2-Amino-3-(4-pyrimidinyl)propenoic Acid (2a, R = H). The hydroxy acid **1a**, (R = H) (20 mmol) in ethanol (100 mL) was treated with ammonium formate (100 mmol) and the reaction mixture was heated under reflux for 4 h. Upon cooling, the product was filtered and crystallized from DMSO, mp > 250 °C dec (65% yield). ^1H NMR (DMSO-d_6): δ 6.00 (1H, s, —CH=), 7.30 (1H, d, H_5), 7.40–7.90 (2H, br s, NH_2), 8.55 (1H, d, H_6), 9.15 (1H, s, H_2); $J_{5,6}$ = 5.5 Hz. Mass spectrum (200 °C) *m/z* (rel intensity): 165 (M^+, 0.43), 121 (0.5), 120 (1.0). Anal. Calcd for $C_7H_7N_3O_2$: C, 50.91; H, 4.27; N, 25.45. Found: C, 51.26; H, 4.21; N, 25.22.

2-Amino-4-carbethoxy-5-(4-pyrimidinyl)thiazole (6a). A solution of the hydroxy ester **1a** (R = Et) (5 mmol) in chloroform (50 mL) was cooled on ice and bromine (1 mL) was added. After 15 min the solvent was removed at reduced pressure and ethanol (20 mL) and thiourea (5 mmol) were added. To the stirred mixture was added *N*-methylmorpholine (0.5 mL), and after about 10 min orange crystals separated. The compound was crystallized from ethanol (65% yield), mp 207–208 °C. ^1H NMR (DMSO-d_6): δ 1.30 (3H, t, CH_2Me), 4.40 (2H, q, CH_2Me), 5.50–5.70 (2H, br s, NH_2), 7.90 (1H, d, H_5), 8.80 (1H, d, H_6), 9.20 (1H, s, H_2); $J_{5,6}$ = 6.0, J_{Et} = 8.0 Hz. Mass spectrum (180 °C) *m/z* (rel intensity): 250 (M^+, 1.0). Anal. Calcd for $C_{10}H_{10}N_4O_2S$: C, 47.99; H, 4.03; N, 22.39. Found: C, 47.56; H, 3.97; N, 21.98.

4,5-Dihydro-5-((4-pyrimidinyl)methylene)-1,2,4-triazin-6(1*H*)-one (5a). To a stirred solution of the compound **4a** (5 mmol) in ethanol (15 mL) was added hydrazine hydrate (5 equiv of 98%). The separated crystals were filtered and crystallized from water (yield 98%), mp > 315 °C. ^1H NMR (DMSO-d_6): δ 6.25 (1H, s, —CH=), 7.45 (1H, dd, H_5), 7.55 (1H, br s, H_3), 8.75 (1H, d, H_6), 9.15 (1H, d, H_2), 11.55–11.75 and 12.00–12.30 (2H, two br s, NH); $J_{5,6}$ = 5.5, $J_{2,5}$ = 1 Hz. Anal. Calcd for $C_8H_7N_5O$: C, 50.79; H, 3.73; N, 37.02. Found: C, 50.80; H, 3.56; N, 37.23.

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