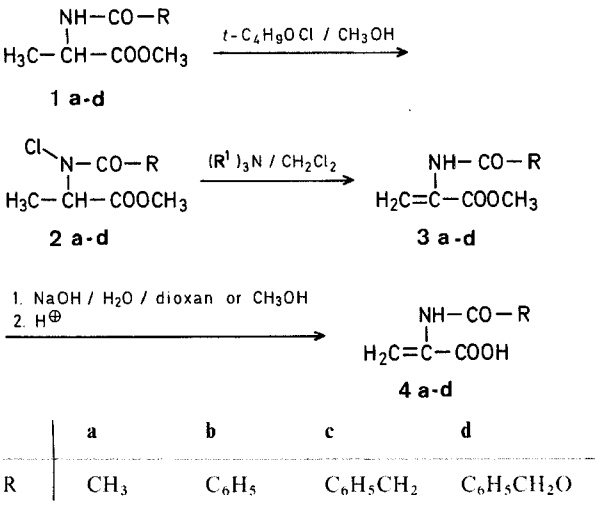

Scheme A

A Convenient, Large-Scale Preparation of 2-Acetamidoacrylic Acid and its Methyl Ester

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We wish to report a convenient, large-scale preparation of 2-acetamidoacrylic acid (**4a**; *N*-acetyldehydroalanine) and of the corresponding methyl ester (**3a**). The method used is an adaptation of Poisel and Schmidt's procedure[1] for preparation of dehydroamino acids via *N*-chloro-*N*-acylamino acid esters and can be carried out on a molar scale.

2-Acetamidoacrylic acid[2] (**4a**) and other 2-acylaminoacrylic acids most commonly have been prepared by methods involving condensation of primary amides with pyruvic acid[3–6]. Reported yields of **4a** prepared by these methods have been in the range[7] of 30–50% and, for most cases, on a scale of approximately 0.2 mol[8]. We have used the procedure of Kil'disheva et al.[4] on a 2.3 mol scale and have obtained **4a** in yields of 28–44%. However, the cost of, and lack of high purity of, commercial pyruvic acid, and also the formation of 2,2-bis[acetamido]propanoic acid as a common side product in the reaction, were factors that caused us to investigate other methods for preparation of **4a**.

Elimination reactions on *O*-tosyl derivatives of serine[9], on sulfonium[10] or sulfinyl[11] derivatives of cysteine, and on β-chloroalanine derivatives[12] have been used to prepare 2-acylaminoacrylic acid esters. While the yields are generally high, most cases reported have been reactions involving millimol quantities.

Poisel and Schmidt[1] recently reported the preparation of dehydroamino acids from *N*-acylamino acid esters by a sequence of *N*-chlorination and elimination. The dehydroamino acids reported by Poisel and Schmidt all contained alkyl substituents in the β-position. We have found the above method to be applicable for preparation of the unsubstituted acrylic acid system and have prepared the acrylic acids as shown in Scheme A.

Only for 2-acetamidoacrylic acid (**4a**) have we carried out the synthesis on a molar scale; the overall yield of **4a** from *N*-acetyl-DL-alanine methyl ester (**1a**) was 58%. The *N*-chlorination of **1a** was effected with *t*-butyl hypochlorite in methanol according to the procedure of Johnson and Greene[13]; *N*-chlorination occurred also under the above conditions with sodium methoxide present as catalyst[14]. The *N*-chlorination procedure of Poisel and Schmidt using *t*-butyl hypochlorite: potassium *t*-butoxide in ether gave incomplete reaction. The elimination-isomerization process on the *N*-chloro derivative **2a** yielded a mixture of the acrylate **3a** and the alanine ester **1a** in a ratio of 4:1. The crude mixture was treated to alkaline hydrolysis, following which the acrylic acid **4a** was readily separated from the more water-soluble *N*-acetyl-DL-alanine. Similar results were obtained in the preparation of the acrylic acids **4b–4d**.

The methyl ester **3a**, rather than being converted to the acid **4a**, can be isolated; this procedure thus affords a convenient preparation of ester **3a**. Previously, **3a** had been prepared by treatment of the silver salt of the acrylic acid **4a** with methyl iodide[5, 12a], by reaction of **4a** with dimethyl sulfate[12a], from *N*-acetylcysteine methyl ester by treatment with silver carbonate[15], and by condensation of acetamidomalonate with formaldehyde[16]. Diazomethane has been used to prepare the methyl ester **3c** from the acid **4c**[9b]. These methods, however, are not readily applicable for the preparation of **3a** on a large scale.

In the method reported herein, ester **3a** can be isolated as an oil in 79% yield following the elimination step simply by effecting an aqueous wash of the product mixture in dichloromethane. Analysis by ^{1}H-N.M.R. indicates this oil to be approximately 95% pure with some *N*-acetyl-DL-alanine methyl ester still present. This material, in most cases, is satisfactory for use in subsequent syntheses. Crystalline **3a** was obtained in 40–55% yield by a procedure involving Kugelrohr distillation and/or recrystallization.

M.p. and b.p. are uncorrected. ^{1}H-N.M.R. spectra were obtained with a Varian EM-360 spectrometer. Thin layer chromatography (T.L.C.) was performed on Quantum Industries Silica Gel MQ6F 1″ × 3″ plates. Evaporations in vacuo were carried out on a Büchler rotatory evaporator. Solvents were routinely dried before use over Linde 3A molecular sieves.

Preparation of Methyl *N*-Acetyl-DL-alaninate (1a; R = CH_3): DL-Alanine (89.1 g, 1.0 mol) is acetylated with acetic anhydride

(160 ml, 1.7 mol) in glacial acetic acid (900 ml) following the procedure of Greenstein and Winitz[17] to give *N*-acetyl-DL-alanine[18], which is isolated as a crude paste. This material is twice taken up in acetone with subsequent removal in vacuo of solvent, dissolved in anhydrous methanol (900 ml) and cooled in an ice bath. Acetyl chloride (80 ml, 1.1 mol) is added slowly to the stirred solution following which the flask is stoppered and the reaction mixture stirred overnight at room temperature. The solvent is removed in vacuo and the residual hydrogen chloride is neutralized by the addition of saturated sodium hydrogen carbonate (150 ml) followed by the addition of solid sodium hydrogen carbonate. The aqueous phase is extracted twice with chloroform (200 ml), saturated with sodium chloride, and again extracted twice with chloroform (200 ml). The combined chloroform extracts are dried ($MgSO_4$) and the solvent removed in vacuo to yield **1a** as an oil. A small amount of lower boiling material is removed under vacuum by heating the oil at 100°/12 torr. The **1a** (139 g, 96%) that remained in the distillation flask is of sufficient purity for use in subsequent reactions. In some cases, **1a** is purified by distillation; 82% yield from DL-alanine; b.p. 78–85°/0.2 torr; m.p. 45–47° from carbon tetrachloride; Lit.[19], b.p. 126–127°/10 torr.

^{1}H-N.M.R. ($CDCl_3$): δ=1.42 (d, 3H, CH_3, J=7 Hz), 2.05 (s, 3H, acetyl), 3.78 (s, 3H, methyl ester), 4.50 (q, 1H, methine), 7.55 ppm (b, 1H, NH).

Preparation of Methyl *N*-Acetyldehydroalaninate (3a; R=CH_3):
Methyl *N*-acetyl-DL-alaninate (**1a**; 97.8 g, 0.67 mol) is dissolved in anhydrous methanol (125 ml) containing a trace of hydroquinone. The resulting solution is stirred at 10–20° in a cold water bath. *t*-Butyl hypochlorite[20] (100 ml, 0.83 mol) is added in one portion followed by the addition of 2 ml of a 1% solution of sodium in methanol. The reaction mixture is stirred at 10–20° for 2 to 4 h, the reaction being followed by T.L.C. (silica gel developed with ethyl acetate). Alternatively, the reaction flask is wrapped with aluminum foil and stored overnight in a refrigerator at ~8°. The excess *t*-butyl hypochlorite and methanol are removed in vacuo at a water bath temperature below 40°. The resulting oil is taken up in dichloromethane (400 ml), washed once with saturated sodium chloride (100 ml), and dried ($MgSO_4$) while being cooled in an ice bath. The filtrate containing the *N*-chloro compound is stored in an ice bath or freezer until ready for use. A sample of the *N*-chloro compound **2a** can be isolated by removal of the solvent in vacuo.

^{1}H-N.M.R. ($CDCl_3$): δ=1.50 (d, 3H, CH_3, J=7 Hz), 2.30 (s, 3H, acetyl), 3.77 (s, 3H, methyl ester), 5.33 ppm (q, 1H, methine).

The above solution is diluted to 1500 ml with dry, alcohol-free dichloromethane[12]. 1,4-Diazabicyclo[2.2.2]octane (DABCO; 75.2 g, 0.67 mol) is added slowly at room temperature to the stirred reaction mixture at a rate that a gentle reflux is maintained. The reaction mixture is stirred an additional 10–20 min until reflux has subsided and then heated at 40–50° in a hot-water bath for 10–20 min with vigorous stirring. The reaction is cooled in an ice bath and the hydrochloride salt is removed by filtration. The organic phase is washed once with water, once or twice with 1 normal hydrochloric acid so that the aqueous phase remains acidic, once with saturated sodium hydrogen carbonate, once with water, and dried over $MgSO_4$.

Triethylamine also can be used as base in which case the *N*-chloroalanine methyl ester in dichloromethane is added in portions at room temperature to neat triethylamine (2 equivalents). After removal of the precipitated hydrochloride salt, the solvent is removed in vacuo, diethyl ether (300 ml) is added to the residue, and the resulting suspension washed as described above.

After drying the organic phase, a trace of hydroquinone is added and the solvent is removed in vacuo. Compound **3a** is obtained in yields of 72–79% as an oil that is shown by ^{1}H-N.M.R. analysis to be at least 95% pure. In some preparations, N.M.R. analysis indicates less than 95% purity and in those cases, the crude oil is dissolved in diethyl ether (400 ml), washed once with water (100 ml), and dried ($MgSO_4$). This process removes the minor component **1a** and provides product **3a** in purity >95%. Compound **3a** of the above purity generally is satisfactory for use in subsequent syntheses.

Crystalline **3a** is obtained by Kugelrohr distillation under high vacuum; hydroquinone is added to both the distillation and receiving flasks to prevent polymerization of **3a**. The distillate is recrystallized from petroleum ether (b.p. 30–60°) to furnish **3a** in yields of 20–40%; m.p. 50–52°; Lit.[5,8], m.p. 52–54°. Product **3a** also can be obtained in crystalline form by initial crystallization of the crude oil from diethyl ether, washing the crystalline material with petroleum ether (b.p. 30–60°), followed by repeated recrystallization from petroleum ether (b.p. 30–60°) to give **3a** in yields 30–55%.

^{1}H-N.M.R. ($CDCl_3$): δ=2.18 (s, 3H, acetyl), 3.83 (s, 3H, methyl ester), 5.83 and 6.57 (2s, 2H, vinyl), 7.85 ppm (b, 1H, NH).

Preparation of 2-Acetamidoacrylic Acid (*N*-Acetyldehydroalanine; 4a; R=CH_3):
Methyl *N*-acetyl-DL-alaninate (**1a**; 97.8 g, 0.67 mol) is converted to the *N*-chloro derivative as described above. The *N*-chloro derivative is treated with DABCO (75.2 g, 0.67 mol) or two equivalents of triethylamine as above. When the reaction is complete, the precipitated hydrochloride salt is removed by filtration and the solvent removed in vacuo. The oily residue is dissolved in dioxan (200 ml) and freshly prepared 1 normal hydroxide (680 ml, 0.68 mol) is added slowly with stirring at room temperature. The mixture is stirred at room temperature for 30–45 min, acidified to pH 2 with concentrated hydrochloric acid, and cooled in ice. The white solid that precipitated is collected by filtration, washed with a small volume of dioxan, and air dried to give **4a**; yield: 51.0 g (58% from **1a**); m.p. 195–196° (dec.); Lit.[4], m.p. 198–199° (dec.). In some cases, product of lesser purity is obtained. This material is purified by recrystallization from methanol following treatment with Norit. A second crop of **4a** can be obtained from the above aqueous filtrate by evaporation of the dioxan in vacuo, cooling the remaining aqueous phase in ice, and collecting the precipitated solid by filtration. Recrystallization of this material from methanol following treatment with Norit gives **4a**; yield: 3.1 g.

^{1}H-N.M.R. (CF_3COOH): δ=2.40 (s, 3H, acetyl), 6.57 and 6.83 (2s, 2H, vinyl), 8.50 ppm (b, 1H, NH).

This reaction has been run many times and on a scale as large as 2 mol. The yields obtained have been regularly in the range of 50–62%.

Preparation of *N*-Acyldehydroalanines (4b-d):
The *N*-acyl-DL-alanine methyl esters (**1b-d**) are prepared as described above for **1a** by methylation of *N*-benzoyl-DL-alanine, *N*-phenylacetyl-DL-alanine[22], and *N*-benzyloxycarbonyl-DL-alanine, respectively. The esters **1b-d** (0.05 mol), used as the crude oil obtained following removal of volatiles at 100°/1.0 torr, are treated with *t*-butyl hypochlorite (0.08 mol) as described for the preparation of **3a**. The Table lists the reaction periods employed for *N*-chlorination; T.L.C. data for compounds **1** and **2** also are given in the Table. The *N*-chloro derivatives **2b** and **2c** are treated with DABCO (one equivalent) or triethylamine (two equivalents) to effect elimination as described for the preparation of **3a**. For **2d**, it is necessary to use triethylamine (two equivalents) or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, one equivalent) as base in the elimination reaction. The elimination reaction is cooled by the addition of ice, washed once with water, once or twice with hydrochloric acid (1 normal), once with saturated sodium hydrogen carbonate, and once with water. After drying ($MgSO_4$), a trace of hydroquinone is added to the dichloromethane solution and the solvent is removed in vacuo.

Table. Preparation and T.L.C. Data for Compounds **2a–d**

Compound 2	Reaction Time at 10–20°	Reaction Time at ~8°	T.L.C. R_f Value 1	T.L.C. R_f Value 2	T.L.C. Solvent
a	2–4 h	8–12 h	0.40	0.72	ethyl acetate
b	6 h	40–48 h	0.36	0.64	chloroform
c	5–6 h	20–24 h	0.47	0.56	ethyl acetate
d	1–2 h	8–12 h	0.50	0.65	chloroform

The crude esters **3b–c** are dissolved in enough dioxan (for **3d**, methanol was used) to produce complete solution after the addition of 1.1 equivalents of freshly prepared sodium hydroxide (1 normal). The reaction mixture is stirred at room temperature for 30–60 min and the organic solvent removed in vacuo. The remaining aqueous solution is acidified to pH 2 with concentrated hydrochloric acid and extracted three times with ethyl acetate (for **4b** and **4c**) or chloroform (for **4d**). The organic extracts are dried ($MgSO_4$) and the solvent removed in vacuo to furnish the dehydroalanines **4b–d** as brown pastes. The paste is dissolved at room temperature in a minimum of ethanol followed by repeated addition of water, cooling, and filtration. The solid obtained is dissolved in the appropriate solvent, treated with Norit, and crystallized to yield pure product.

2-Benzamidoacrylic acid (**4b**; $R=C_6H_5$); yield: 39% from **1b**; m.p. 161–163° (from ethanol/water), Lit.[4], m.p. 158–160°.

^{1}H-N.M.R. (CF_3COOH): $\delta=6.60$ and 6.97 (2s, 2H, vinyl), 7.70 (m, 5H, aryl), 8.80 ppm (b, 1H, NH).

2-Phenylacetamidoacrylic acid (**4c**; $R=C_6H_5CH_2$); yield: 33% from **1c**; m.p. 179–181° (from ethanol/water), m.p. 187–189° (from ethyl acetate); Lit.[9b], m.p. 185–186°.

^{1}H-N.M.R. (CF_3COOH): $\delta=3.97$ (s, 2H, benzyl), 6.45 and 6.80 (2s, 2H, vinyl), 7.45 (s, 5H, aryl), 8.38 ppm (b, 1H, NH).

N-Benzyloxycarbonyldehydroalanine (**4d**; $R=C_6H_5CH_2O$); yield: 40% from **1d**; m.p. 107–109° (from dichloromethane/petroleum ether, b.p. 30–60°): Lit.[9a], m.p. 108–109°.

^{1}H-N.M.R. ($CDCl_3$): $\delta=5.20$ (s, 2H, benzyl), 6.00 and 6.37 (2s, 2H, vinyl), 7.33 (b, 1H, NH), 7.40 ppm (s, 5H, aromatic).

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