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Branko S. Jursic [a], Sarada Sagiraju [a], Dustin K. Ancalade [a], Traneil Clark [a] & Edwin D. Stevens [a]

[a] Department of Chemistry, University of New Orleans, New Orleans, Louisiana

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Practical Preparation of *Z*-α-(*N*-Acetylamino)- and *Z*-α-(*N*-Benzoylamino)-α,β-unsaturated Acids

Branko S. Jursic, Sarada Sagiraju, Dustin K. Ancalade, Traneil Clark, and Edwin D. Stevens
Department of Chemistry, University of New Orleans, New Orleans, Louisiana

Abstract: An efficient two-step synthetic procedure for the preparation of numerous variations of *N*-protected α,β-unsaturated α-amino acids and their corresponding esters from *N*-protected glycine and either aliphatic or aromatic aldehydes was developed. The reaction involved cyclization of the *N*-protected glycine into oxazolone, condensation with the aldehyde, and ring opening with a base.

Keywords: acylaminocinnamic acid, azlactone condensation, azlactone ring opening, azalactones, oxazolones

Amino acid derivatives are compounds of high commercial importance.[1] A variety of asymmetric synthetic methods for amino acid preparation have been developed. One method of importance involves hydrogenation of an enamide using chiral transition-metal catalysts. Perhaps one of the best examples using enamides as a starting material[2] is enantioselective synthesis of [(*S*)-2-amino-3-(3,4-dihyroxyphenyl)propanoic acid] (L-DOPA),[3] which involves a rhodium hydrogenation catalyst containing a chiral phosphorus ligand reacting with an enamide.

Unfortunately, large-scale manufacturing of α,β-unsaturated amino acids has proven to be problematic. Theoretically, amino acids are ideal starting

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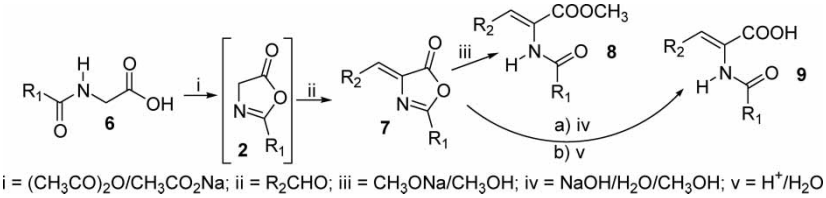
Address correspondence to Branko S. Jursic, Department of Chemistry, University of New Orleans, New Orleans, LA 70148. E-mail: bjursic1@uno.edu

materials in the preparation of these compounds. For instance, L-threonine methyl ester is an excellent starting material in the preparation of Z-2-(*N*-acetylamino) butenoate.[4] However, there is no general synthetic procedure using amino acids as precursors. Here we present a general synthetic procedure for the preparation of large quantities of α-acetylamino- and α-benzoylamido-α,β-unsaturated acids.

N-Protected glycine and the corresponding aldehydes were chosen as the optimal starting reagents for these reactions. To fully understand and demonstrate the scope of this condensation, the reaction progression between *N*-acetylglycine (**1**) and 1,4-benzenedicarbaldehyde (**3**) was followed by NMR spectroscopy (Fig. 1). The first step is the formation of 2-methyl-4*H*-oxazol-5-one (**2**), which readily condenses with **3** to form the monocondensation product **4**. The reaction continues, and the final double condensation product **5** is formed. According to our NMR studies, the conversion appears to be nearly quantitative. Similar reaction conditions were used for the preparation of oxazolones **7** (Table 1).

The oxazolone ring is exceptionally easy to open with either hydroxy or alcoxy ions, which produces the corresponding acids or esters, respectively. This approach was used for quantitative preparations of esters **8** or acids **9** (Table 1).



i = $(CH_3CO)_2O/CH_3CO_2Na$; ii = R_2CHO; iii = CH_3ONa/CH_3OH; iv = $NaOH/H_2O/CH_3OH$; v = H^+/H_2O

To determine the stereochemistry of the double bond generated in the course of the condensation reaction, X-ray structural analysis was performed with **7g** (Fig. 2). X-ray analysis proved that this isomer was the major isomer (more than 95%) of the condensation reaction. Our X-ray crystallographic study confirms that the stereochemistry of the major isomer formed during condensations of **2** with aldehyde has *Z*-configuration of the newly formed double bond of **7**. Therefore, in preparation of both esters **8** and acids **9**, which are prepared by ring opening of **7**, stereochemistry of the double bond must be preserved.

We developed a successful method for the preparation of *Z*-2-acetamido and *Z*-2-benzamido-2,3-unsaturated acids and their methyl esters starting from *N*-protected glycine. The starting materials are inexpensive, and the reaction procedures are very simple, therefore it is applicable to large-scale (industrial) preparation of these valuable intermediates for use in the pharmaceutical industry.

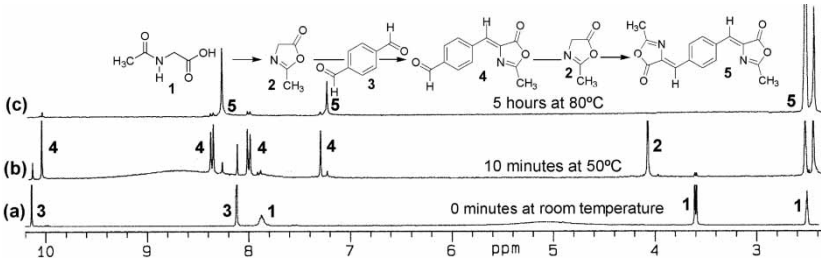


Figure 1. NMR data of reaction following experiment for preparation of **5**.

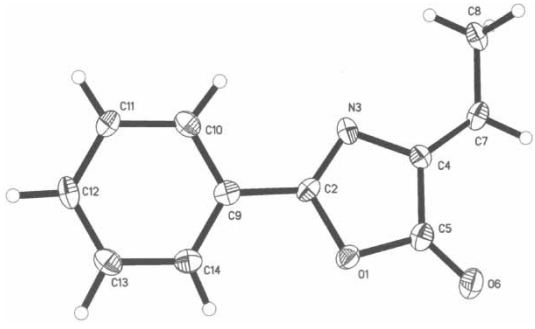


Figure 2. Ortep drawing of the X-ray determined structure of **7g**.

EXPERIMENTAL

All NMR reactions following experiments were performed on 500-MHz Unity500 Varian NMR instrument by taking samples from the reaction

Table 1. Isolated yields

R_1	R_2	**7**	Yield of **7**	**8**	Yield of **8**	**9**	Yield of **9**
CH_3	n-C_8H_{17}	**7a**	70	**8a**	70	**9a**	87
CH_3	C_6H_5	**7b**	90	**8b**	90	**9b**	93
CH_3	3,4,5-$(MeO)_3C_6H_4$	**7c**	92	**8c**	82	**9c**	96
CH_3	4-$(Me_2N)C_6H_4$	**7d**	93	**8d**	90	**9d**	88
CH_3	1-naphthyl	**7e**	80	**8e**	80	**9e**	92
CH_3	2-furyl	**7f**	90	**8f**	89	**9f**	96
C_6H_5	CH_3	**7g**	95	**8g**	90	**9g**	91
C_6H_5	n-C_8H_{17}	**7h**	87	**8h**	87	**9h**	98
C_6H_5	Ph	**7i**	90	**8i**	90	**9i**	96
C_6H_5	3,4,5-$(MeO)_3C_6H_4$	**7j**	80	**8j**	80	**9j**	93
C_6H_5	4-$(Me_2N)C_6H_4$	**7k**	90	**8k**	90	**9k**	91
C_6H_5	1-naphthyl	**7l**	84	**8l**	87	**9l**	92
C_6H_5	2-furyl	**7m**	92	**8m**	91	**9m**	89

mixture containing 0.02 mol of *N*-acetylglycine, 20 mL of acetic anhydride, 3 g of sodium acetate, and 0.01 mol of 1,4-benzenedicarbaldehyde. The NMR sample was prepared as DMSO-d_6 solution. All DMSO-d_6 samples were clear solutions. Elemental analysis was performed by Atlantic Microlab, Inc. X-ray structure determination was performed on Bruker Smart 1KCCD automated diffractometer. Crystals of compound **7g** were obtained by slow crystallization from a diluted methanol solution of **7g**. The monocrystal needle of **7g** for X-ray study was tricilinic with P-1 symmetry space group. Dimensions of **7g** crystal were a = 3.8583(10) Å, b = 10.957(3) Å, c = 11.692(3) Å, $\alpha = 68.628(9)^\circ$, $\beta = 80.577(7)^\circ$, $\gamma = 82.749(7)^\circ$. Cell formula unit is $Z = 2$. Computation of X-ray data collection and the cell refinement were performed by Bruker Smart. Computation of X-ray data reduction was performed by Bruker Saint. Computation of structure solution and structure refinement from X-ray data were performed by SHELXL-97. Our ^{1}H NMR spectroscopic data for compounds **7b**, **7i**, **7k**, and **7m** are in agreement with previously reported NMR data.[5]

General Procedure for Preparation of Oxazolone 7: Preparation of 2-Methyl-4-(3,4,5-trimethoxybenzylidene)-4H-oxazol-5-one (7c)

A suspension of *N*-acetylglycine (5.9 g; 0.05 mol), sodium acetate (4.1 g; 0.05 mol), and acetic anhydride (30 mL) was stirred at room temperature for 30 min. Into the white suspension, 3,4,5-trimethoxybenzaldehyde (8.3 g; 0.05 mol) was added. The resulting suspension was stirred at room temperature for 1 h and then at 60°C for 5 h. The reaction mixture became a brown solution that upon cooling to room temperature again became a suspension. This suspension was mixed with water (1 L) and stirred at room temperature for a half an hour. The insoluble material was separated by filtration, washed with water (3 × 30 mL), and recrystallized from methanol (~250 mL) to afford 12.8 g (92%) of product. Mp 153–155°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (2H, s), 6.94 (1H, s), 3.87 (3H, s), 3.86 (6H, s), and 2.33 ppm (3H, s). ^{13}C NMR ($CDCl_3$) δ 167.8, 165.7. 153.1, 141.0, 131.7, 131.2, 128.6, 109.6, 61.0, 56.1, and 15.7 ppm. Anal. calcd. for $C_{14}H_{15}NO_5$ (MW 277.27): C, 60.64; H, 5.45; N, 5.05. Found: C, 60.58; H 5.53, N 4.96.

General Procedure for Preparation of 8: Preparation of Methyl (Z)-2-Benzoylaminobut-2-enoate (8g)

The methanol (20 mL) solution of **7g** (1.87 g; 0.01 mol) and sodium methoxide in methanol (2 mL of 25% CH_3ONa in CH_3OH) was stirred at room temperature for 15 min. Solvent was evaporated, and the residue was partitioned between 10% aqueous ammonium chloride (100 mL) and methylene chloride (150 mL). The organic layer was washed with water (3 × 100 mL), dried over anhydrous sodium sulfate, and evaporated to an

oily residue. The oily residue was dissolved in hot petroleum ether (500 mL) from which white needles of product crystallized. The yield of the product was 1.97 g (90%). Mp 70–72°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (2H, d, $J = 7.2$ Hz), 7.63 (1H, broad s), 7.54 (1H, t, $J = 7.2$ Hz), 7.46 (2H, t, $J = 7.2$ Hz), 6.89 (1H, q, $J = 7.6$ Hz), 3.78 (3H, s), and 1.84 ppm (2H, d, $J = 7.6$ Hz). ^{13}C NMR ($CDCl_3$,) δ 165.4, 165.1 (two carbonyls), 133.9, 133.8, 132.0, 128.6, 127.4, 126.0 (six alkene carbons), 52.4 (CH_3 carbon), and 15.0 ppm (CH_2 carbon). Anal. calcd. for $C_{12}H_{13}NO_3$ (MW 219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.57; H 6.05, N 6.26.

General Procedure for Preparation of 9: Preparation of 2-Acetylamino-3-phenylacrylic Acid (9b)

Into aqueous (200 mL) sodium hydroxide (4.0 g; 0.1 mol), a solution of methanol (200 mL) and 4-benzylidene-2-methyl-4H-oxazol-5-one (18.7g; 0.1 mol) was added. The reaction mixture was stirred at room temperature for 30 min, followed by methanol evaporation at reduced pressure. The remaining clear water solution was acidified with 10% hydrochloric acid to pH ~3 and left at room temperature overnight. The formed crystalline product was separated by filtration, washed with cold water (3 × 50 mL) and dried at 110°C for 30 min to afford pure product. The yield of the reaction was 19.1 g (93%). Mp 188–190°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.5 (1Hm s, NH), 7.62 (2H, d, $J = 7.2$ Hz), 7.41 (2H, t, $J = 6.0$ Hz), 7.35 (1H, t, $J = 7.2$ Hz). 7.24 (1H, s, CH), and 1.91 ppm (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 169.4 and 166.5, 133.8, 131.2, 129.8, 129.2. 128.6, 127.5, and 22.6 ppm. Anal. calcd. for $C_{11}H_{11}NO_3$ (MW 205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.26; H, 5.49; N, 6.89.

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