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Stereoselective Synthesis of (*Z*)-2-Acylamido-4-phenylcrotonates

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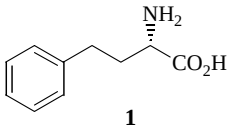
Abstract: Two practical methods for highly stereoselective synthesis of (*Z*)-2-acylamido-4-phenylcrotonates **2a~b** have been developed. The key step in the first route was how to control the acid-catalyzed isomerization of condensation mixtures of α-keto ester **5** with carbomite. In the second route the key step was reduction of oxime **8**, derived from α-keto ester **5**, with iron powder in the presence of acetic anhydride.

Keywords: (*Z*)-α,β-Dehydroamino acids, stereoselective synthesis, $E \rightarrow Z$ isomerization, Fe/Ac_2O reduction of oxime.

Stereospecific synthesis of (*Z*)-α,β-dehydroamino acids is of great importance in the preparation of uncommon or natural optically pure amino acids, because, in general, (*Z*)-isomers afford much higher enantioselectivities with faster rates than (*E*)-isomers in the catalytic asymmetric hydrogenation[1]. (*Z*)-isomers of ethyl 2-acylamido-4-phenyl crotonate **2** are important precursors in the course of our synthesis of L-homophenyl alanine **1**, a key synthon for most commercially important antihypertensive ACE inhibitors such as Enalapril, Benazepril, Lisinopril. Herein we reported two highly stereoselective approaches to (*Z*)-2-acylamido-4-phenylcrotonate **2a~b**.



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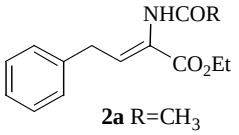
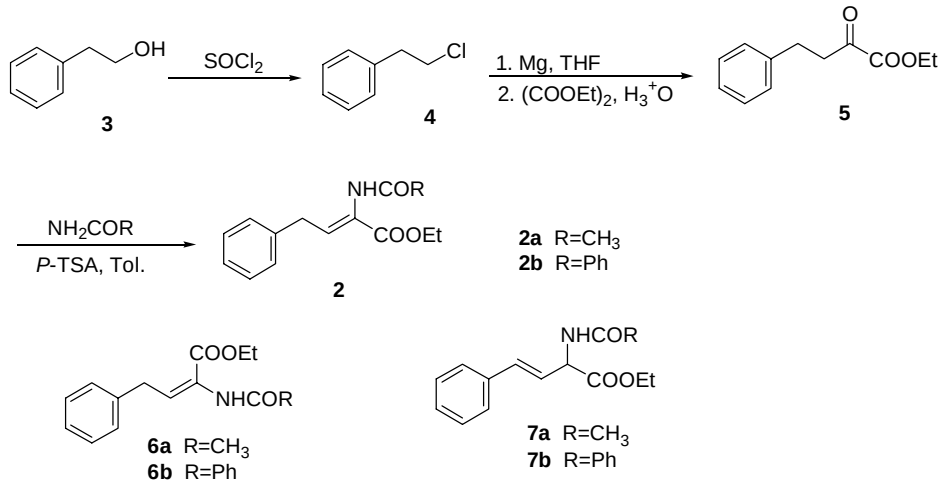


2a R=CH_3
2b R=Ph

In the presence of *p*-toluenesulfonic acid, the condensation of 2-oxo-4-phenyl butanoate **5**, derived from 2-phenylethyl alcohol **3**[2,3], with acetamide gave a mixture of *Z*-olefin **2a**, *E*-olefin **6a** and tautomer β,γ-dehydroamino acid ester **7a** (**Scheme 1**). It seems that the content of **2a** increases as the ratio of acetamide to α-keto ester **5** decreases. When a ratio of 3:1 of acetamide to α-keto ester **5** was used, the desired **2a** was obtained only in 26%, whereas a ratio of 1.5 : 1 led to 49% of **2a** (**Table 1**, entries 1~3). Under the same reaction condition, the condensation of α-keto ester **5** with benzamide gave the similar result, with 53% of (*Z*)-**2b** (**Table 1**, entry 4). It is extremely difficult to separate discrete isomers by column chromatography because of their similar polarities. In addition, the hydrogenation of tautomers **7a** and **7b** could only give D,

L-homophenylalanine. To avoid this drawback and based on the work of Cativlela C.[4] that (*E*)-isomers of α,β-dehydroamino acid could be converted to the thermodynamically more stable (*Z*)-isomers by Lewis acid $TiCl_4$, we investigated several acid catalysts for the conversion of not only (*E*)- **6a**, **6b** but also tautomers **7a**, **7b** to (*Z*)- **2a**, **2b**.

Scheme 1



First, we tested direct treatment of condensation mixtures with Lewis acids and HCl gas (**Table 1**). HCl gas gave better conversion than Lewis acid $TiCl_4$ and $AlCl_3$. The best results were 65% of **2a** and 88% of **2b** when treated with HCl at 80 °C, and the isolated yields of **2a** and **2b** were 30% and 68%, respectively.

Table 1. Acid-catalyzed isomerization of condensation products

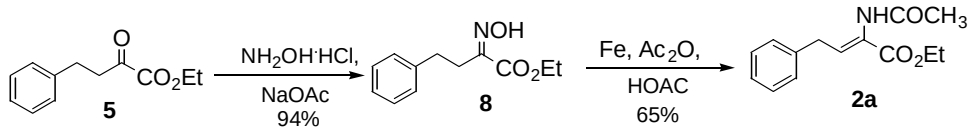
Entry	R	Condensation Product **2 : 6 : 7**			Conversion Condition	Result **2 : 6 : 7**		
1	CH_3	49	23	28	$TiCl_4$, CH_2Cl_2, r.t., 24 h	60	9	31
2	CH_3	49	23	28	$AlCl_3$, CH_2Cl_2, r.t., 78 h	55	18	28
3	CH_3	26	53	21	HCl (gas), 80 °C, 7 h	65	9	26
4	C_6H_5	53	30	17	HCl (gas), 80 °C, 2 h	88	1	11

Under above acid-catalyzed condition, the yield of **2a** was not satisfactory, and our further investigation of the conversion of discrete isomers **6a** and **7a** showed that the tautomer **7a** could only be partially isomerized to (*Z*)-**2a** under various catalytic conditions (**Table 2**). This observation led us to seek alternative stereoselective method to (*Z*)-**2a**.

Table 2. Acid-, base-catalyzed isomerization of discrete isomers **6a** and **7a**

Entry	R	Substrate	Conversion Condition	Result **2 : 6 : 7**		
1	CH_3	**6a**	$TiCl_4$, CH_2Cl_2, r.t., 73 h	97	3	
2	CH_3	**7a**	$TiCl_4$, CH_2Cl_2, r.t., 160 h	unchanged		
3	CH_3	**6a**	piper., diox., 60 °C or r.t., 6 h	49	2	49
4	CH_3	**7a**	piper., diox., 60°C or r.t., 6 h	49	2	49

In 1998 Burk[5] and Zhang[6], separately, reported two similar methods for the preparation of enamides *via* reduction of oximes with iron powder in the presence of acetic anhydride. We now extended this method to accommodate α, β- dehydroamino acid derivatives and actually got a satisfactory result. (*Z*)-**2a** was obtained in > 92% stereoselectivity, with merely 7% of (*E*)-**6a** and trace tautomer **7a** (<1%). Only single recrystallization, instead of previous tedious column chromatography, gave (*Z*)-**2a** in 65% yield. Presently we are extending this process to the syntheses of other α,β-dehydroamino acid derivatives, including those bearing different *N*-acyl groups, in order to establish the generality of this potentially useful method.



In conclusion, highly stereoselective synthesis of (*Z*)-2-acylamido-4-phenyl crotonates has been achieved: acid-catalyzed isomerization of condensation mixtures for (*Z*)-ethyl 2-benzamido-4-phenylcrotonate **2b**, and reduction of oxime, derived from α-keto ester **5**, with iron powder in the presence of acetic anhydride for (*Z*)-ethyl 2-acetamido-4-phenylcrotonare **2a**.

All of the new compounds were identified by IR, MS, ^{1}H-NMR (300 MHz or 400 MHz, in $CDCl_3$) and elemental analysis[7].

Acknowledgment

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References and notes

1. B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.*, **1977**, *99*, 5946.
2. D. G. Mellio, R. D. Larsen, D. J. Mathre, W. F. Shukis, A.W. Wood, J. R. Colleluori, *J. Org. Chem.*, **1987**, *52*, 5143.
3. G. A. Olah, R. D. Porter, *J. Am. Chem. Soc.*, **1971**, *93*, 6877.
4. C. Cativlela, M. D. Villegas, *Tetrahedron*, **1993**, *49*, 497.
5. M. J. Burk, G. Casy, N. B. Johsons, *J. Org. Chem.*, **1998**, *63*, 6084.
6. G. Zhu, A. L. Casalnuovo, X. M. Zhang, *J. Org. Chem.*, **1998**, *63*, 8100.
7. The spectral analytical and physical data of new compounds.

Compd	mp℃	IR cm^{-1}	MS	1H NMR	Elemental Analysis
2a	86-87	1728, 1659	M^++1: 248	δ 1.27 (t, 3H, *J*=7.2,$OCH_2\underline{CH_3}$), 2.15 (s, 3H, $COCH_3$), 3.50 (d, *J*=7.0, 2H, H-4), 4.29 (q, 2H, *J*= 7.2, $O\underline{CH_2}CH_3$), 6.83 (t, 1H, *J*= 7.0, H-3), 7.06 (br s, 1H, NH), 7.19-7.30 (m, 5H, Ph)	Anal. Calcd: C, 68.00; H, 6.91; N, 5.66 Found: C, 67.55; H, 6.86; N, 5.53

6a	oil.	1724, 1669	M^++1: 248	δ 1.27 (t, 3H, *J*=7.1,OCH_2 $\underline{CH_3}$), 2.08(s, 3H, $COCH_3$), 3.93 (d, 2H, *J*=7.0, H-4), 4.33 (q, 2H, *J*=7.1, $O\underline{CH_2}CH_3$), 7.35-7.18 (m, 6H, Ph, H-3), 7.44 (br s, 1H, NH)	
7a	82-84	1750, 1644	M^++1: 248	δ 1.29 (t, 3H, *J*=7.0,$OCH_2\underline{CH_3}$), 2.08 (s, 3H, $COCH_3$), 4.28-4.18 (m, 2H, $O\underline{CH_2}CH_3$), 5.27 (t, 1H, *J*=7.0, H-2), 6.18 (dd, 1H, *J*=15.6, *J*=6.4, H-3), 6.32 (d, 1H, *J*=7.2, NH), 6.63 (d, 1H, *J*=16.0, H-4), 7.36-7.23 (m, 5H, Ph)	Anal. Calcd: C, 68.00; H, 6.91; N,5.66 Found: C, 68.46; H, 6.78; N, 5.61
2b	97-98	1724, 1643	91(100)	δ 1.29 (t, 3H, *J*=7.0,$OCH_2\underline{CH_3}$), 3.59 (d, 2H, *J*=7.2, H-4), 4.24 (q, 2H, *J*=7.2, $O\underline{CH_2}CH_3$), 6.92 (t, 1H, *J*=7.2, H-3), 7.73-7.21 (m, 5H, 4-Ph), 7.75-7.57 (m, 3H, PhCO), 7.71 (br s, 1H, NH), 7.86(m, 2H, PhCO)	Anal.Cacld: C, 73.77; H, 6.19; N, 4.53 Found: C, 74.01; H, 6.22; N, 4.62
6b	oil	1729, 1667	M^+: 309	δ 1.39 (t, 3H, *J*=7.2,$OCH_2\underline{CH_3}$), 4.02 (d, 2H, *J*=8.0, H-4), 4.39 (q, 2H, *J*=7.1, $O\underline{CH_2}CH_3$), 7.32-7.20 (m, 4H, PhCO, H-3), 7.59-7.43 (m, 5H, 4-Ph), 7.82-7.79 (m, 2H, PhCO), 8.29 (br s, 1H, NH)	
7b	105-107	1742, 1656, 1639	M^+: 309	δ 1.32 (t, 3H, *J*=7.2,$OCH_2\underline{CH_3}$), 4.28 (m, 2H, $O\underline{CH_2}CH_3$), 5.47 (t, 1H, *J*=6.4, H-2), 6.29 (dd, 1H, *J*=16.0, *J*=6.0, H-3), 6.72 (d, 1H, *J*=16.0, H-4), 6.95 (d, 1H, *J*=6.8, NH), 7.55-7.25 (m, 8H, PhCO, 4-Ph), 7.86 (d, 2H, Ph CO)	Anal. Calcd: C, 73.77; H, 6.19; N, 4.53 Found: C, 73.50; H, 6.30; N, 4.93
8	90-92	3244, 1726	M^+: 221	δ 1.33 (t, 3H, *J*=7.0,OCH_2 $\underline{CH_3}$), 2.87-2.85 (m, 2H, Ph $\underline{CH_2}$), 2.96-2.91 (m, 2H, $PhCH_2$ $\underline{CH_2}$), 4.28 (q, 2H, *J*=7.1, $O\underline{CH_2}$ CH_3), 7.32-7.20 (m, 5H, Ph)	Anal. Calcd: C, 65.14; H, 6.83; N, 6.33 Found: C, 65.12; H, 6.89; N, 6.25

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