C–N Bond Cleavage of Benzylic Enaminones in the Presence of Acetyl or Aroyl Chlorides: A Novel One-Pot Synthesis of *N*-Acetyl or *N*-Aroyl β-Benzylidene α-Amino Acid Esters

Abdolali Alizadeh,*[a] Hamideh Sabahnoo,[a] Nasrin Zohreh,[a] Zohreh Noaparast,[a] Long-Guan Zhu[b]

[a] Department of Chemistry, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Iran
Fax +98(21)88006544; E-mail: abdol_alizad@yahoo.com; E-mail: aalizadeh@modares.ac.ir

[b] Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China

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Abstract: Benzylic enaminones generated by addition of benzylamines to dialkyl acetylenedicarboxylates are trapped in situ by chloroacetyl or aroyl chlorides in refluxing toluene. Good yields of *E*-isomers of *N*-acetyl or *N*-aroyl α-amino acid esters were produced exclusively via C–N bond cleavage and C–C bond formation resulting from a 1,3-benzyl shift.

Key words: enaminone, benzylic enaminone, aroyl chloride, chloroacetyl chloride, α-amino acid ester, C–N bond cleavage

α-Amino acid derivatives are the fundamental building blocks of peptides, proteins and many natural products and play essential roles in living organisms.[1] Unnatural amino acids, particularly synthetic α-amino acids have also played a significant role in the area of peptide research having been used extensively in peptide analogues to limit conformational flexibility, enhance enzymatic stability and improve pharmacodynamics and bioavailability.[2] For example, salicylanilide esters of a-amino acid ester **1** have shown high antimicrobial activity[3] and aspartame (**2**) is an artificial sweetener, used as a sugar substitute in some foods and beverages (Figure 1). In addition, such substrates represent a subclass of building blocks that may be used to make stereochemically complex targets such as peptides and valuable heterocycles.[4]

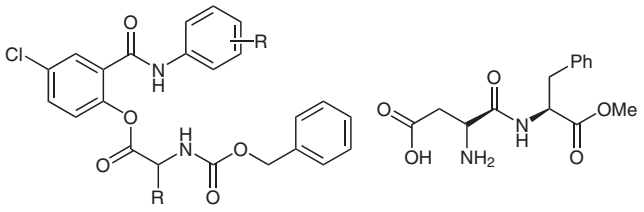

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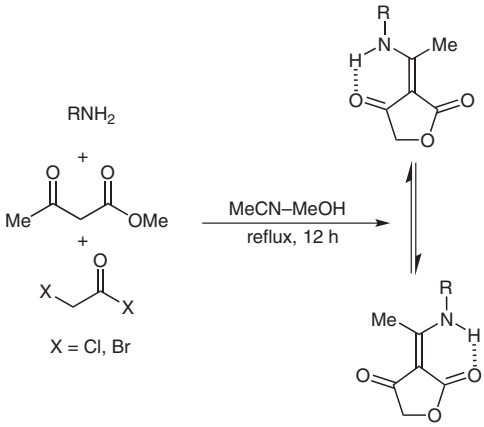
Figure 1 Examples of valuable compounds with N-protected α-amino acid ester substructure

Application of enaminones as ambident 1,3-binucleophilic intermediates in synthetic organic chemistry[5] and especially in heterocyclic synthesis is well documented.[6] There are many reports on functionalization of enaminones in the literature by introduction of different substituents on the nitrogen, the α-carbon and the β-carbonylic carbon atoms for preparation of various heterocyclic systems including some natural products and analogues.[7]

Recently, our research group reported a novel synthesis of α-alkylidene-γ-butyrolacton-2-ones (tetronic acids) from the reaction of primary amines, methyl acetoacetate and chloroacetyl chloride or its bromo analogue (Scheme 1).[8]



Scheme 1 Synthesis of α-alkylidene-γ-butyrolacton-2-ones (tetronic acids) from chloroacetyl chloride or bromoacetyl bromide[8]

Along the same lines, we have become interested in application of dialkyl acetylenedicarboxylates in place of acetoacetic esters. To the best of our knowledge, there has been no investigation into the reaction of benzylic enaminones with chloroacetyl chloride. Thus, in continuation of our previous work on using enaminones,[9] in this letter we report a straightforward approach to *N*-chloroacetyl or *N*-aroyl β-benzylidene α-amino acid esters via a one-pot process.

As shown in Scheme 2, the one-pot optimized equimolar reaction of benzylamine, dimethyl acetylenedicarboxylate and chloroacetyl chloride proceeded smoothly in toluene under reflux to produce *N*-chloroacteyl β-benzylidene α-amino acid ester **5b** after eight hours in 76% yield.

To investigate the reaction scope and limitations, different types of amine were used in the reaction under the same condition. As depicted in Table 1, the reaction of benzylamine **3**, dialkyl acetylenedicarboxylate **4** and chloroacetyl chloride is general with regards to the benzylamine

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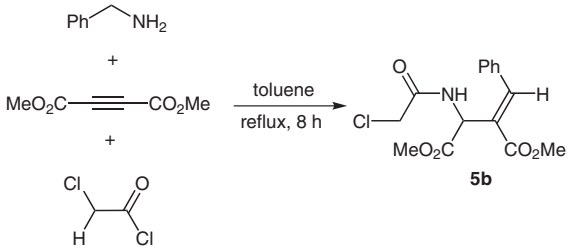
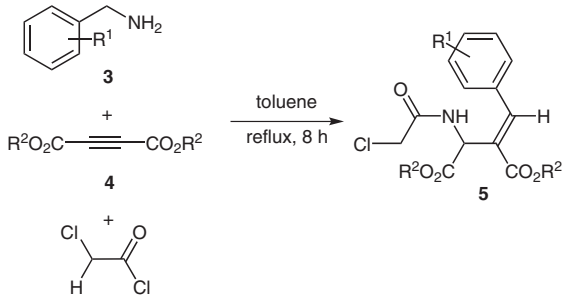


Scheme 2 Reaction of benzylamine, dimethyl acetylenedicarboxylate and chloroacetyl chloride in toluene

Table 1 Synthesis of *N*-Chloroacetyl β-Benzylidene α-Amino Acid Ester Derivatives



Product	R^1	R^2	Yield (%)
5a	*p*-Cl	Me	80
5b	H	Me	76
5c	*p*-Me	Me	71
5d	*o*-Cl	Et	75
5e	H	Et	72
5f	*p*-MeO	Et	65

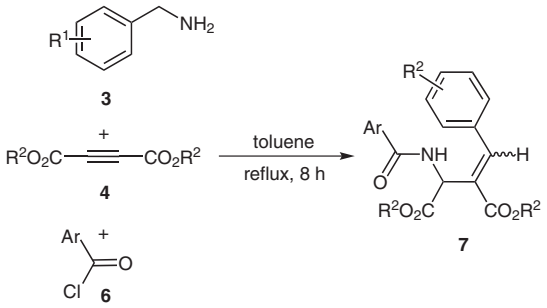
component. In addition, the product yield increases with electron-withdrawing groups on the phenyl moiety (Table 1).

Regarding the efficiency of the reaction, aroyl chlorides were also employed to study the substrate scope. As expected, reaction of benzylamines **3**, dialkyl acetylenedicarboxylate **4** and aroyl chlorides **6** proceeded smoothly at reflux in toluene to produce *N*-aroyl β-benzylidene α-amino acid esters **7** (Table 2).

The structures of **5a–f** and **7a–g** were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. For example, in the IR spectrum of **5a**, stretching frequencies of NH, two C=O of esters and amidic C=O appeared at 3430, 1738, 1706 and 1652 cm^{-1}, respectively.

Almost all mass spectra of compounds **5** and **7** displayed [M$^+$] or [M$^+$ + 1] peaks at the appropriate value. In the ^{1}H NMR spectra, two doublets at about δ = 5.50–6.50 and 7.50–7.80 ppm (the latter exchangeable with D_2O on heating) related to the CHNH moiety, and a sharp singlet at around δ = 8.00 ppm due to C=CH, are characteristic signals for the compounds **5** and **7**. ^{13}C NMR spectra of all compounds **5** and **7** showed a NHCH signal at around δ = 50 ppm while the CH_2Cl signal in compound **5** appeared at about δ = 42 ppm. The vinylic carbons for both of compounds **5** and **7** resonate at δ = 40–44 ppm. Finally, results of single crystal X-ray diffraction analysis of **5c** indicated the *E* orientation of substitution around C=C (*E*-isomer) in addition to confirming of the proposed gross structure (Figure 2).[10]

Table 2 Synthesis of *N*-Aroyl β-Benzylidene α-Amino Acid Ester Derivatives



Product	R^1	R^2	Ar	Yield (%)
7a	H	Me	*p*-$NO_2C_6H_4$	85
7b	H	Me	*p*-ClC_6H_4	82
7c	H	Me	*p*-BrC_6H_4	80
7d	Me	Et	*p*-$NO_2C_6H_4$	78
7e	*p*-OMe	Me	*p*-$NO_2C_6H_4$	78
7f	*p*-OMe	Me	*p*-ClC_6H_4	76
7g	*p*-OMe	Me	*p*-BrC_6H_4	74

Although no detailed mechanistic and experimental investigations have been carried out, a plausible reaction sequence to the products is outlined in Scheme 3. On the basis of the established chemistry of enaminones,[8,9,11]

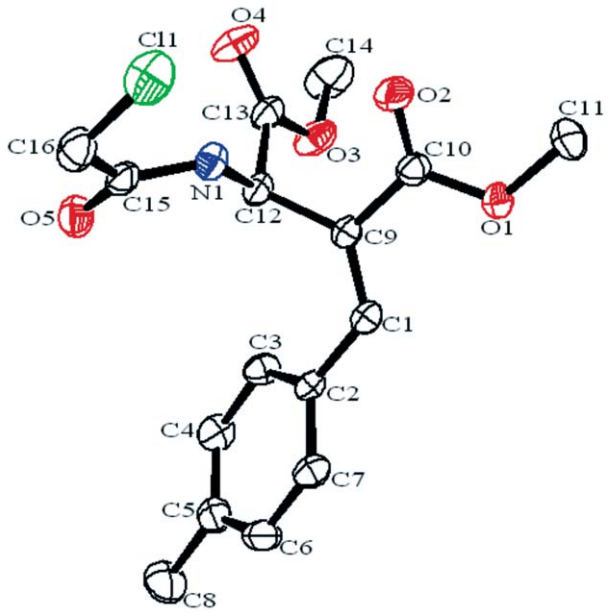
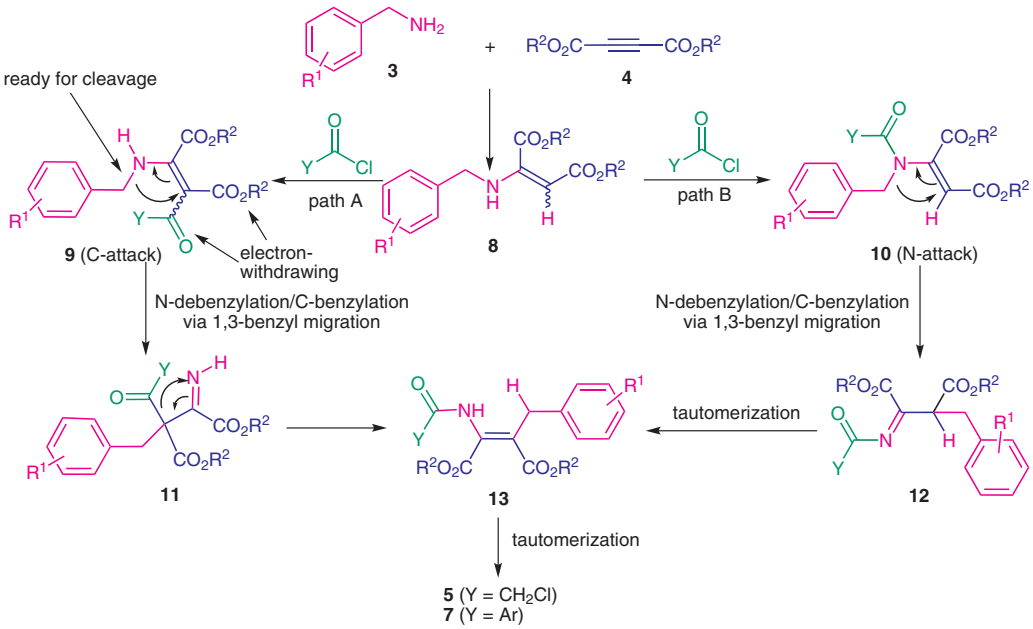


Figure 2 X-ray crystal structure of compound **5c**



Scheme 3 Plausible mechanism for the formation of *N*-chloroacetyl or *N*-aroyl β-benzylidene α-amino acid esters **5** and **7**

compounds **8** apparently results from addition of the primary amines **3** to the dialkyl acetylenedicarboxylate **4**. In the presence of the acid halide, enaminone C- or N-acylation occurs to afford push-pull enaminone **9** or amido enaminone **10**.[12] The key step involves conversion of compound **9** or **10** to **11** or **12** via C–N bond cleavage followed by 1,3-benzyl migration to afford intermediate **11** or **12**. The next step involves 1,3-acyl or 1,3-aroyl shift in **11** or tautomerization in **12** to produce intermediate **13**. Finally, intermediate **13** converts to the *N*-acetyl or *N*-aroyl β-benzylidene α-amino acid esters **5** or **7** via a final tautomerization.

In conclusion, a novel, convenient and efficient one-pot synthesis of *N*-acetyl or *N*-aroyl β-benzylidene α-amino acid esters is reported from readily available and inexpensive starting materials. It is proposed that the reaction proceeds via C–N bond cleavage resulting from benzyl migration; a novel behavior for *N*-benzyl enaminones. All of the reactions are stereoselective for the *E*-alkene. The reaction also allows the introduction of three diversity points into the final amino acid. From a structural viewpoint, all of the products are similar to aspartic acid Figure 3). Other notable features of this reaction include easy reaction performance, purification and good yield. Further investigations on the reaction mechanism, scope and limitations are underway.

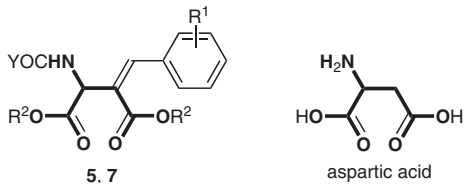


Figure 3

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(10) **Typical Procedure**: To a magnetically stirred 5-mL flat-bottom flask containing benzylamine (0.22 g, 2 mmol) and toluene as solvent was added dimethyl acetylenedicarboxylate (0.28 g, 2 mmol). After 30 min, a solution of chloroacetyl chloride (0.37 g, 2 mmol) for **5a** or *p*-nitrobenzoyl chloride (0.44 g, 2 mmol) for **7a** was added to the reaction mixture and stirring was allowed to continue at 100–120 °C for 8 h. After the completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane–EtOAc, 9:1) to obtain **5a** and crystallized from Et_2O to obtain **7a**. Compound **5a** was obtained as a yellow oil (0.28 g, yield: 80%). IR (KBr): 3430 (NH), 1738 (CO_2Me), 1706 (CO_2Me), 1652 (NC=O) cm^{-1}. ^1H NMR (500.13 MHz, $CDCl_3$): δ = 3.77 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 4.04 (AB system, $^3J_{H,H}$ = 15.2 Hz, 2 H, CH_2Cl), 5.75 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, CHN), 7.33–7.35 (m, 2 H, 2 × CH of Ar), 7.44–7.46 (m, 1 H, CH of Ar), 7.55–7.57 (m, 1 H, CH of Ar), 7.68 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, NH), 8.01 (s, 1 H, s, C=CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 42.37 (CH_2Cl), 49.97 (CHN), 52.59 (OMe), 53.19 (OMe), 127.09 (CH of Ar), 128.84 (*C*=CH), 129.75 (CH of Ar), 130.07 (CH of Ar), 130.71 (CH of Ar), 132.61 (C_{ipso}-Cl), 134.20 (C_{ipso}-C=C), 141.62 (C=*C*H), 165.36 (CON), 166.50 (*C*O_2Me), 169.71 (*C*O_2Me). MS (EI, 70 eV): *m*/*z* (%) = 324 (15), 296 (69), 268 (71), 236 (73), 207 (63), 125 (100), 111 (74). Anal. Calcd for $C_{15}H_{15}Cl_2NO_5$: C, 50.02; H, 4.20; N, 3.89. Found: C, 50.00; H, 4.17; N, 3.87. Compound **5c**: white powder (0.24 g, yield: 71%); mp 82–85 °C. IR (KBr): 3425 (NH), 1761 (CO_2Me), 1697 (CO_2Me), 1670 (NC=O) cm^{-1}. ^1H NMR (500.13 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, Me), 3.76 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 4.05 (AB system, $^3J_{H,H}$ = 15.2 Hz, 2 H, CH_2Cl), 6.01 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, CHN), 7.24 (d, $^3J_{H,H}$ = 7.9 Hz, 2 H, 2 × CH of Ar), 7.40 (d, $^3J_{H,H}$ = 8.0 Hz, 2 H, 2 × CH of Ar), 7.69 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, NH), 7.95 (s, 1 H, C=CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 21.39 (Me), 42.41 (CH_2Cl), 49.87 (CHN), 52.36 (OMe), 53.06 (OMe), 126.33 (*C*=CH), 129.17 (2 × CH of Ar), 129.63 (2 × CH of Ar), 130.95 (C_{ipso}-C=C), 139.98 (C_{ipso}-Me), 144.55 (C=*C*H), 165.41 (CON), 167.13 (*C*O_2Me), 170.05 (*C*O_2Me). MS (EI, 70 eV): *m*/*z* (%) = 340 (64) [M^+ + 1], 280 (80), 248 (100), 172 (57), 157 (53), 144 (52), 129 (44), 105 (6), 91 (24), 77 (27), 59 (22). Anal. Calcd for $C_{16}H_{18}ClNO_5$: C, 56.56; H, 5.34; N, 4.12. Found: C, 56.53; H, 5.32; N, 4.90. Crystal data for **5c** (CCDC 695674): $C_{16}H_{18}ClNO_5$, MW = 339.76, triclinic, space group *P*21/*n*, a = 13.5932 (12) Å, b = 7.9447 (7) Å, c = 16.5222 (15) Å, α = 90°, β = 106.461 (1)°, γ = 90°, V = 1711.2 (3) $Å^3$, Z = 4, Dc = 1.319 mg/m^3, F(000) = 712, crystal dimension: 0.31 × 0.26 × 0.23 mm, radiation, Mo Kα (λ = 0.71073 Å), 1.72≤2*c*≤25.18, intensity data were collected at 295 (2) K with a Bruker APEX area-detector diffractometer, and employing ω/2*c* scanning technique, in the range of –16≤h≤15, –9≤k≤9, –19≤l≤19; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2546 observed reflections with R(into) = 0.0734 by a full-matrix least-squares technique converged to R = 0.0614 and Raw = 0.1475 [I >2σ(I)]. Compound **7a**: cream powder (0.34 g, yield: 85%); mp 118–120 °C. IR (KBr): 3333 (NH), 1752 (CO_2Me), 1694 (CO_2Me), 1668 (NC=O), 1603 (C=C), 1484, 1342 (NO_2) cm^{-1}. ^1H NMR (500.13 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 6.19 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, CHN), 7.43 (d, $^3J_{H,H}$ = 7.2 Hz, 1 H, NH), 7.47 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, 2 × CH_{meta} of Ph), 7.49 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH_{para} of Ph),7.57 (d, $^3J_{H,H}$ = 7.3 Hz, 2 H, 2 × CH of Ph), 7.94 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, 2 × CH of Ar), 8.02 (s, 1 H, C=CH), 8.26 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 2 × CH of Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 50.32 (CHN), 52.50 (OMe), 53.25 (OMe), 123.78 (2 × CH of Ar), 127.17 (*C*=CH), 128.44 (2 × CH of Ar), 128.94 (2 × CH of Ar), 129.13 (2 × CH of Ar), 129.74 (CH of Ar), 133.82 (C_{ipso}-C=C), 139.42 (C_{ipso}-CON), 144.56 (C=*C*H), 149.80 (C_{ipso}-NO_2), 164.58 (CON), 167.36 (*C*O_2Me), 170.30 (*C*O_2Me). MS (EI, 70 eV): *m*/*z* (%) = 399 (8) [M^+ + 1], 366 (16), 339 (79), 307 (100), 279 (5), 248 (16), 173 (17), 150 (75), 120 (12), 104 (33), 92 (16), 76 (18), 59 (7). Anal. Calcd for $C_{20}H_{18}N_2O_7$ (398.37): C, 60.30; H, 4.55; N, 7.03. Found: C, 60.28; H, 4.52; N, 7.01.

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