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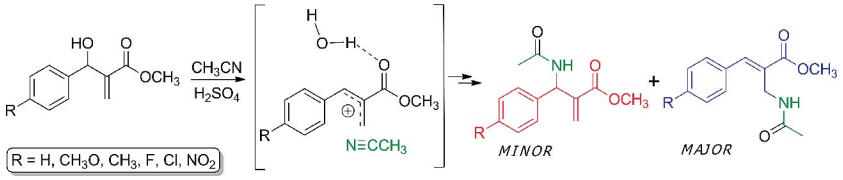
Reaction Mechanisms



Acid-mediated solvolysis of α-methylene-β-hydroxy esters in acetonitrile to give isomeric allylic acetamides has been investigated. Two pathways for nucleophilic attack, at the terminal methylene or at the benzylic carbon, were identified; both pathways involve an allylic cation, with the lowest activation energy associated with an S_N1'-type mechanism.

M. M. Sá,* M. Ferreira, G. F. Caramori, L. Zaramello, A. J. Bortoluzzi, D. Faggion Jr., J. B. Domingos* 1–9

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Investigating the Ritter Type Reaction of α-Methylene-β-hydroxy Esters in Acidic Medium: Evidence for the Intermediacy of an Allylic Cation

Marcus M. Sá,*[a] Misael Ferreira,[a] Giovanni F. Caramori,[b] Laize Zaramello,[b] Adailton J. Bortoluzzi,[c] Deonildo Faggion Jr.,[d] and Josiel B. Domingos*[d]

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The acid-mediated solvolytic transformation of α-methylene-β-hydroxy esters in acetonitrile was investigated. The reaction was shown to involve nucleophilic attack either at the terminal methylene or at the benzylic carbon. Kinetic and theoretical studies were performed to elucidate the possible pathways involved in the formation of the acetamide products, i.e., through an addition-elimination mechanism, a concerted process (S_N2 and S_N2'), or involving an allylic cation (S_N1 and S_N1'). The results of the kinetic analysis, including the isotope effect, Hammett plot, and Eyring plot, are in agreement with a proton transfer equilibrium prior to the formation of a benzylic carbenium ion intermediate, which is consistent with a unimolecular stepwise mechanism. Theoretical examination at the DFT level of theory corroborated these findings, with the lowest activation energy being associated with the S_N1'-type mechanism.

Introduction

The chemistry of allylic derivatives and the propensity of their nucleophilic substitution reactions to result in rearranged products have been the subject of intensive study for over a century.[1–3] However, the exact structures of the possible products formed, as well as their relative distribution, are often rather unpredictable because they are dependent on the allylic substrate and on a range of reaction variables. Therefore, detailed mechanistic studies have been carried out to understand this transformation at such a level that it should be possible to control the reaction profile. Consequently, a diverse array of mechanisms have been proposed for the nucleophilic substitution involving allylic derivatives. These include S_N1-type (through the intermediacy of an allylic cation or a closely related intimate ion pair), S_N2'-type (by nucleophilic displacement with concomitant double-bond migration), stepwise addition-elimination (wherein a stabilized carbanion is invoked), as well as combinations of these.[4–6]

Although these contributions sum up the current scenario, many points of controversy or general uncertainty and several unanswered questions still remain. Due to the particularities of the allylic substitution, the product structure (and the mechanisms involved in this transformation) cannot be reliably anticipated on the basis of similarities with previously reported reactions. Further investigation is needed to rationalize the mechanistic intricacies. Unfortunately, such detailed studies are not available for nucleophilic reactions involving α-methylene-β-hydroxy esters, ketones and nitriles **B** (Scheme 1).

Perhaps the most explored allylic framework of all time, allylic alcohols **B** are widely employed as building blocks for the stereoselective synthesis of a great variety of biologically relevant heterocycles and natural products.[7] This versatile class of compounds is readily available from the Morita–Baylis–Hillman reaction, an organocatalyzed coupling of aldehydes with α,β-unsaturated esters, ketones or nitriles that represent a 100%-atom-economy process. Besides the overwhelming amount of research on the Morita–Baylis–Hillman reaction, which can be inferred from the number of recent reviews and reports published in this creative area of research,[8] only a few papers have been dedicated to defining the mechanistic aspects of nucleophilic substitution reactions involving the allylic backbone characteristic of the Morita–Baylis–Hillman adducts.[9–12]

The multifunctional allylic alcohol **B** can formally participate as a Michael acceptor for the conjugate addition of suitable nucleophiles (hydride, halides, sulfinates) to give rearranged **P′**-type products, which are valuable synthetic

[a] MESOLab - Laboratório de Metodologia e Síntese Orgânica, Departamento de Química, Universidade Federal de Santa Catarina,
Florianópolis, SC 88040-900, Brazil
E-mail: marcus.sa@ufsc.br
Homepage: http://www.ufsc.br
[b] GEEM - Grupo de Estrutura Eletrônica Molecular
Departamento de Química, Universidade Federal de Santa Catarina,
Florianópolis, SC 88040-900, Brazil
[c] Laboratório de Cristalografia, Departamento de Química, Universidade Federal de Santa Catarina,
Florianópolis, SC 88040-900, Brazil
[d] LaCBio - Laboratory of Biomimetic Catalysis, Departamento de Química, Universidade Federal de Santa Catarina,
Florianópolis, SC 88040-900, Brazil
E-mail: josiel.domingos@ufsc.br
http://www.ufsc.br
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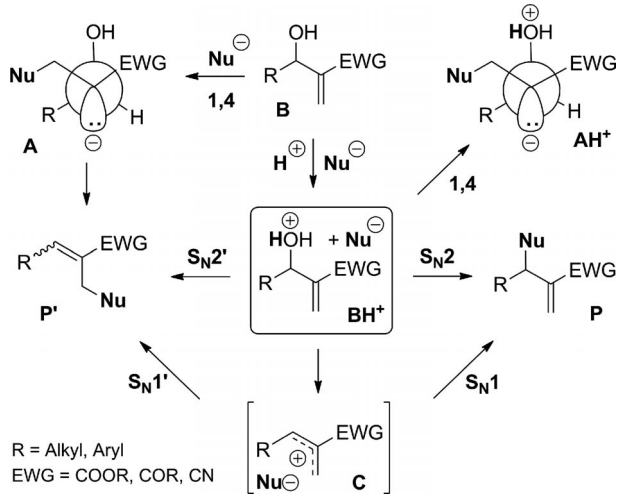


Scheme 1. Conceivable mechanisms for nucleophilic substitution in the allylic scaffold.

intermediates[13,14] (Scheme 1). Although the mechanistic outcome for the reactions carried out under basic or nearly neutral conditions has not been explored in detail, it is generally accepted that initial nucleophilic 1,4-addition followed by an elimination step from the intermediate **A** operates in these cases, rather than merely an S_N1'- or S_N2'-type process. Therefore, the stereoselectivity observed for the double bond in **P′**, which is dependent on the electron-withdrawing group (EWG), could be explained by steric effects associated with the substitution pattern in **A**.[14] Clearly, when the nucleophilic displacement (by halides, nitrate or acetonitrile) occurs under acid catalysis, this proposal for the mechanism would not hold because the formation of anionic intermediate **A** would be unlikely to occur in an environment with a high concentration of H^+ (Scheme 1). Nonetheless, some authors[15–19] propose the intermediacy of a protonated species $\mathbf{AH^+}$ (a simple variant of **A**) in acidic medium to give rearranged **P′** after the elimination of water as a suitable leaving group. In fact, acid-mediated nucleophilic substitutions through an S_N1-type reaction, by the intermediacy of carbenium ion **C** or related ionic pairs, has only occasionally been proposed for allylic alcohols.[20,21]

During the development of a simple and general method to prepare (*Z*)-allylic bromides[22] by treating **1** with a combination of lithium bromide and sulfuric acid in acetonitrile at room temp.,[23] we found that acetamides **2** and **3** (obtained from a Ritter type[16,24–27] reaction with the solvent) were competitively formed when LiBr was replaced by less soluble sodium or potassium bromide. Our interest in synthetic transformations involving allylic alcohols **B**[28] and in mechanistic studies on nucleophilic reactions[29] prompted us to undertake an in-depth investigation of the acid-mediated solvolytic nucleophilic substitution reaction involving the α-methylene-β-hydroxy esters **1** with acetonitrile to give the corresponding mixture of allylic acetamides **2** and **3** (Scheme 2). Herein, we describe and discuss in detail our full experimental and theoretical results, which we hope will contribute to a better understanding of the behavior of multifunctionalized allylic motifs.

Results and Discussion

Synthesis

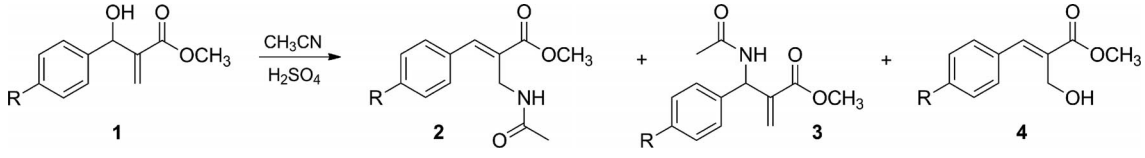
Allylic acetamides **2** and **3** (Scheme 2) were prepared by the acid-mediated Ritter reaction of α-methylene-β-hydroxy esters **1** in the presence of an excess of acetonitrile (used as the solvent). Reaction times, product ratios, and yields for representative aryl-substituted acetamides are presented in Table 1. The consumption of **1** was monitored by TLC and complete conversion into the expected products was readily achieved for more electron-rich substrates (entries 2 and 3), whereas those substituted with electron-withdrawing groups led to slower transformations (entries 5 and 6). In all reactions studied, a mixture of isomeric acetamides **2** and **3** was obtained. In most cases, minor amounts of allylic alcohol **4**[30] were also detected (except for cases detailed in entries 2 and 6), which could be readily separated out by filtration through a plug of silica gel.

Table 1. Experimental conditions for the synthesis of allylic acetamides **2** and **3** from the solvolysis of α-methylene-β-hydroxy esters **1**.[a]

Entry	R	Time [h]	Ratio [%] **2/3/4**[b]	Yield [%] **2/3**[c]	Yield [%] **2**[d]
1	H	1	55:35:10	57 [1.6:1]	20
2	CH_3O	0.5	92:8: < 1	85 [10:1]	60
3	CH_3	0.5	60:32:8	75 [1.9:1]	30
4	F	0.5	57:33:10	55 [1.7:1]	25
5	Cl	3	55:33:12	50 [1.6:1]	25
6	NO_2	120[e]	70:30: < 1	48 [2.3:1]	15

[a] Reaction conditions: **1** (1.0 mmol), H_2SO_4 (2.5 equiv.), MeCN (3.0 mL), 0→25 °C. [b] The relative product distribution (%) was determined by integration of suitable peaks in the ^1H NMR spectrum (400 MHz, $CDCl_3$) of the crude reaction mixture. [c] Yield after column chromatography; rearranged alcohol **4** was also isolated in up to 10% yield. [d] Yield after column chromatography followed by crystallization (CH_2Cl_2) of the major isomer **2**. [e] H_2SO_4 (5.0 equiv.) was used.

The ratio of isomeric acetamides **2/3** varied depending on the ring substitution, however, preferential formation of isomer **2** was observed in all cases. An acceptable level of



Scheme 2. Acid-mediated Ritter type reactions of α-methylene-β-hydroxy esters **1** with acetonitrile (R = H, CH_3O, CH_3, F, Cl, NO_2).

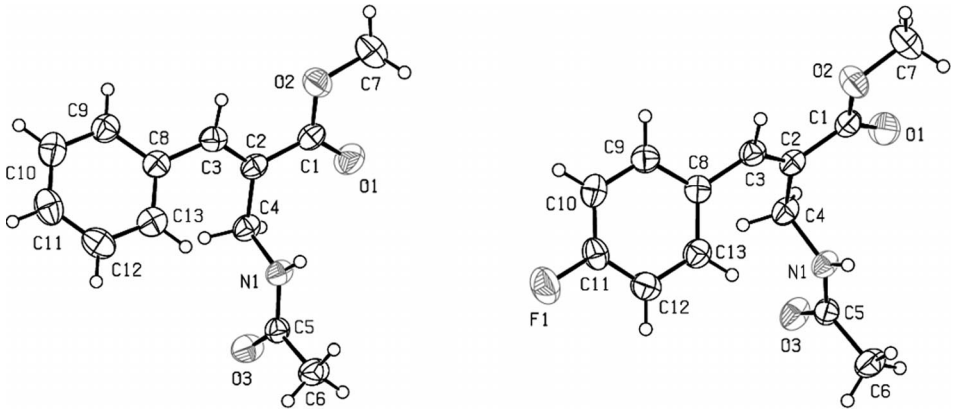


Figure 1. ORTEP plot of acetamides **2a** (R = H; left) and **2d** (R = F; right); ellipsoids are drawn at the 40% probability level.

selectivity was only achieved when the aromatic ring was substituted with a strongly electron-donating R group (Table 1, entry 2). Due to the propensity of allylic alcohols **1** to undergo a variety of transformations involving migration of the double bond,[7,8] it is surprising to find no mention of the competitive formation of isomeric acetamide **3** in related Ritter type reactions of **1** reported in the literature.[16,20a,27]

Although complete chromatographic separation of isomeric acetamides **2** and **3** could not be achieved at this stage, the major isomer **2** was selectively isolated in fair yields after crystallization from CH_2Cl_2 (Table 1). The unequivocal structural elucidation of allylic acetamides **2a** and **2d** was further confirmed by single-crystal X-ray crystallographic analysis (Figure 1; see also the Supporting Information). These compounds are isostructural and both structures show perfect stacking of molecules along the crystallographic c-axis. Furthermore, the presence of the intermolecular N–H···O hydrogen bond leads to the formation of a one-dimensional polymeric structure parallel to the [001] direction.

To check whether any of the detected products **2**–**4** might be a reaction intermediate (i.e., if one product can be converted into any other under the acidic reaction conditions), control reactions were performed with acetamide **2d**, acetamide **3d** (in a 6:1 mixture with **2d**), and allylic alcohol **4d**, which were separately treated with acetonitrile and H_2SO_4 at room temp. for several hours. After the usual aqueous work-up, each compound was recovered unchanged and no interconversion or decomposition in the reaction medium was observed in any of the cases.

Further analysis of the reaction profile was achieved by running the Ritter type reaction of **1** directly in an NMR tube for various reaction times (see the Supporting Information). Formation of the three expected products **2**–**4** with simultaneous consumption of substrate **1** was evidenced in the first few minutes, immediately after the addition of H_2SO_4 to a solution of **1** in CD_3CN. The reaction reached completion (> 95% conversion by NMR spectroscopic analysis) three hours later to give **2/3/4** in ratios that were similar to those given in Table 1.

Mechanistic Analysis and Kinetic Data

The mechanism of the acid-mediated solvolysis reactions of α-methylene-β-hydroxy esters **1** in acetonitrile (Scheme 2) was investigated by means of kinetic and theoretical approaches. The reaction kinetics were monitored spectrophotometrically by measuring the appearance of major acetamide products **2**, which show distinct spectral profiles with maximum absorptions at around 270 nm. The reaction obeyed pseudo-first-order kinetics for at least three half-lives. Figure 2 shows the dependence of the reaction of **1a** (R = H; see the Supporting Information for R = CH_3O, CH_3, F, and Cl) on the acid concentration, with a linear correlation between k_{app}, the pseudo-first-order rate constant, and the concentration of sulfuric acid.

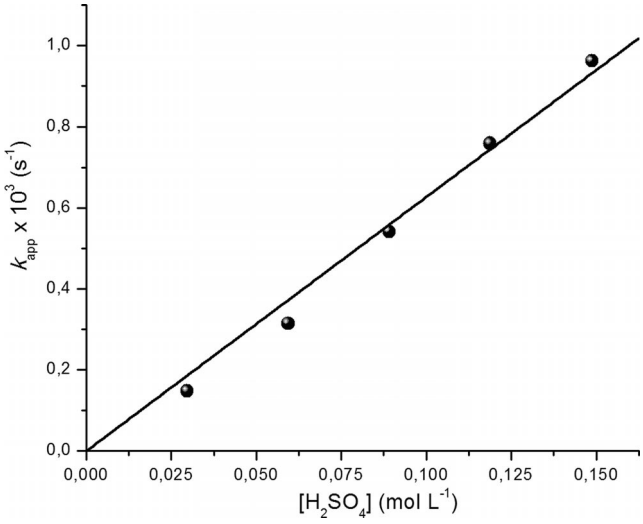


Figure 2. Acid-mediated solvolysis reactions of α-methylene-β-hydroxy ester **1a** (R = H) in acetonitrile at 25 °C.

The apparent second-order rate constants k_H were determined from the slopes of these correlation curves. As shown in Table 2, the reaction rates were greatly increased by the introduction of electron-donating substituents at the *para*-position. However, because the substitution pattern can affect either pre-equilibrium protonation or a subsequent

rate-controlling step with the formation of a positively charged intermediate, a reaction pathway involving the **BH⁺** intermediate (Scheme 1) cannot be kinetically distinguished at this point.

Table 2. Apparent second-order rate constant for the acid-catalyzed solvolysis of α-methylene-β-hydroxy esters **1a**–**f** in CH_3CN at 25 °C.

Entry	1[a]	R	k_H ($L\,mol^{-1}\,s^{-1}$)
1	**1a**	H	5.8×10^{-3}
2	**1b**	CH_3O	9.5×10^{2}
3	**1c**	CH_3	0.1
4	**1d**	F	8.7×10^{-3}
5	**1e**	Cl	1.5×10^{-3}

[a] It was not possible to observe the formation of any product from **1f** (R = NO_2) under the experimental conditions of the kinetic studies.

To ascertain whether the protonation step is rate-controlling, the solvent kinetic isotope effect was determined for the solvolysis of the unsubstituted α-methylene-β-hydroxy ester **1a**. It was observed that changing the acid catalyst from H_2SO_4 to D_2SO_4 led to a small inverse solvent kinetic isotope effect of $k_{H(H)}/k_{H(D)} = 0.91$, which is typical of reactions proceeding with a rapid protonation in pre-equilibrium.

In addition, the rate constants shown in Table 2 are well-correlated in the Hammett plot with the appropriate Hammett substitution constants (Figure 3). Whereas ordinary σ constants did not correlate with the experimental data, a rather satisfactory linear correlation with the σ+ values was obtained, giving a reaction constant, ρ, of –6.5. These data suggest that, in the transition state, electron-donating groups stabilize the positive charge developed at the benzylic carbon through direct resonance interaction, which is consistent with a stepwise mechanism.

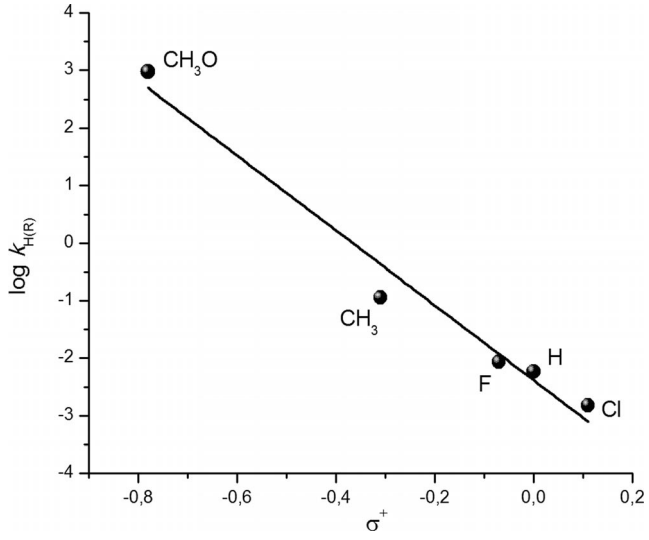
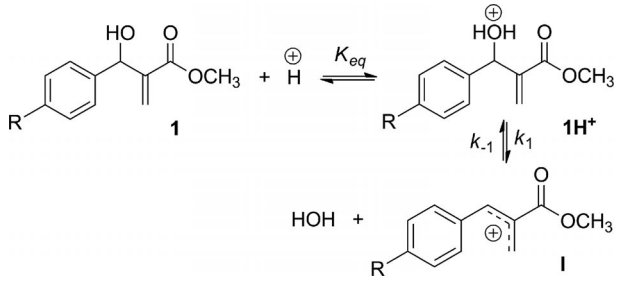


Figure 3. Hammett plot for the solvolysis reaction of α-methylene-β-hydroxy esters **1** in acetonitrile at 25 °C (R = H, CH_3O, CH_3, F, Cl).

These results strongly support the hypothesis of a rate-controlling step involving the formation of a carbenium ion intermediate, as expected for the unimolecular pathway (Scheme 3). In this case, the second-order rate constant k_H is the product k_1K_{eq}, where k_1 is the rate constant for the formation of the carbenium ion intermediate **I** and K_{eq} is the equilibrium constant for the protonation of the α-methylene-β-hydroxy ester **1**.



Scheme 3. Generation of carbenium ion **I** (R = H, CH_3O, CH_3, F, Cl).

The effect of temperature on the reaction rate was studied over a range of 25–65 °C. The experimental entropy of activation ($\Delta S^{\ddagger} = -37.2\,J\,mol^{-1}\,K^{-1}$) was obtained from an Eyring plot (Figure 4). The negative sign of the observed entropy of activation is typical of solvolysis processes, indicating an extensive reorganization of the solvent shell in the transition state as a result of the solvation of ions. In addition, the magnitude of the entropy of activation is indicative of a unimolecular rather than bimolecular reaction, which normally presents larger negative values in solvolytic reactions (ca. –60 to –80 $J\,mol^{-1}\,K^{-1}$).[31]

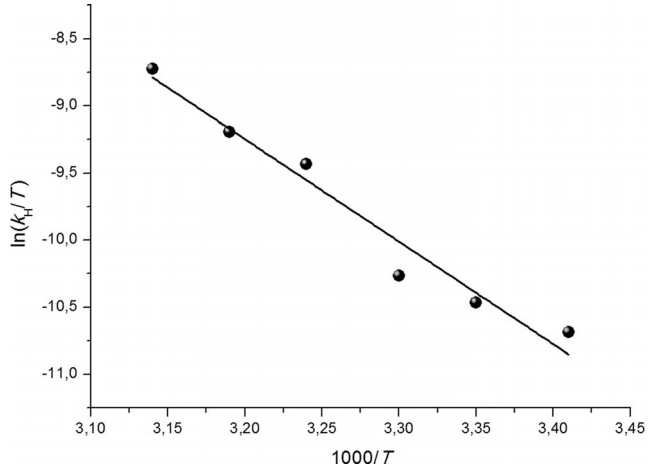
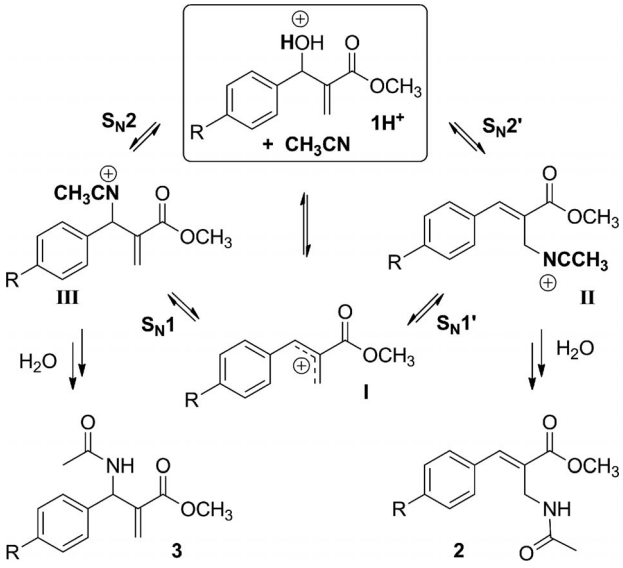


Figure 4. Eyring plot for the solvolysis reaction of α-methylene-β-hydroxy ester **1a** (R = H), in acetonitrile from 25 to 65 °C.

Mechanistic Analysis and Theoretical Investigation

Possible mechanisms for the formation of nitrilium cations **II** and **III** from protonated α-methylene-β-hydroxy esters **1H⁺** (Scheme 4) were also investigated through the determination of the intrinsic reaction coordinate (IRC),[32] the minimum energy pathway connecting reactants to products via a transition state. All calculations were performed with the Gaussian03 package,[33a] using the B3LYP[33b,33c]/

TZVP[33d,33e] level of theory. Three representative substrates were chosen based on the substitution pattern of the aryl R group, wherein R = CH_3O represents an electron-donating group (**1b**), R = NO_2 an electron-withdrawing group (**1f**), and R = H for the unsubstituted control (**1a**).



Scheme 4. Mechanistic representation of possible pathways for the solvolysis reaction of protonated α-methylene-β-hydroxy esters **1H**$^+$ in acetonitrile (R = H, CH_3O, NO_2).

Scheme 4 illustrates the four mechanisms under study that are related to the participation of a carbenium ion intermediate (by S_N1 vs. S_N1') or to a concerted nucleophilic substitution process (by S_N2 vs. S_N2'). According to Scheme 4, two possible sites (C1 and C3) are envisioned for nucleophilic attack on the allylic moiety regardless of whether the mechanism involves a stepwise process or a bimolecular displacement. Further transformation of intermediates **II** and **III** into the corresponding allylic acetamides **2** and **3** under hydrolytic conditions is a well-established process and was not addressed in this mechanistic study.

Analysis of the energy barrier for each of the four solvolytic pathways originating from the protonated α-methylene-β-hydroxy esters **1H**$^+$ (Scheme 4) allowed estimation of the activation energy (E_a) in most cases (Table 3). In the case of the S_N2 mechanism (entries 1, 5, and 9), it was not possible to observe a single transition state for the conversion of the substrate into the product, even after an exhaustive search. Consequently, no further examination was performed for this mechanism. Even though the activation energy values for the alternative S_N2'-type bimolecular mechanism could be calculated in the three cases (entries 2, 6, and 10), they were much higher than the values found for the stepwise mechanisms (entries 3, 4, 7, 8, 11, and 12). These data endorse the stepwise mechanisms over the unfavorable simultaneous displacement of the leaving group by acetonitrile.

Table 3. Activation energies (E_a) according to the type of reaction mechanism and substitution pattern (R).

Entry	R	Mechanism type	E_a [kcal mol^{-1}]
1	H	S_N2	not found
2	H	S_N2'	21.50
3	H	S_N1	12.72
4	H	S_N1'	10.13
5	CH_3O	S_N2	not found
6	CH_3O	S_N2'	21.72
7	CH_3O	S_N1	7.67
8	CH_3O	S_N1'	4.61
9	NO_2	S_N2	not found
10	NO_2	S_N2'	21.36
11	NO_2	S_N1	13.71
12	NO_2	S_N1'	11.27

It is also important to note that, of the two possible stepwise processes (S_N1 and S_N1'), S_N1' is predicted to be prevalent in all cases (compare Table 3, entries 3 and 4; 7 and 8; 11 and 12), giving the corresponding allyl acetamides **2** via intermediate **II** as the major isomer, in agreement with the observed experimental data (see Table 1). The concordance between the theoretical and experimental results involving the isomeric ratio of **2**/**3** supports the possibility that the product distribution is controlled kinetically, given that no equilibration between **2** and **3** takes place under the reaction conditions (see above).

The energy diagram for the stepwise mechanisms (S_N1 vs. S_N1') in the solvolysis reaction of unsubstituted α-methylene-β-hydroxy ester **1a** (R = H) is shown in Figure 5. The energy diagrams for the substituted analogues **1b** (R = CH_3O) and **1f** (R = NO_2) show similar profiles, with minor changes in the bond lengths and the geometries (see the Supporting Information for R = CH_3O and NO_2). For instance, the effect of the electron-donating group reflects the expected capacity of each substituent to stabilize a positive charge, with the methoxy group presenting a much lower energy barrier in relation to the other cases studied. The results of these theoretical studies provide a good fit with the experimental findings in which α-methylene-β-hydroxy ester **1b** (R = CH_3O) is approximately 2×10^5 times more reactive than **1a** (R = H).

Finally, the preferential formation of allylic acetamide **2** (through an S_N1'-type mechanism) over acetamide **3** (through an S_N1-type mechanism) could also be predicted from the theoretical results. Natural bond orbital (NBO) population analysis of the transition states TSIIA and TSIIIA (Figure S16 of the Supporting Information) revealed that the most stabilizing interactions involving occupied and nonoccupied NBOs are the N lone pair of acetonitrile, $LP_{(N)} \rightarrow p_{(C)}$, and the π-type conjugative delocalizations $\pi_{(CC)} \rightarrow p_{(C)}$, which are more stabilizing in TSIIA than in TSIIIA. Conjugative delocalizations involving NBOs from ester moieties [$\pi_{(CO)} \rightarrow \pi^*_{(CC)}$] and [$\sigma_{(CO)} \rightarrow \sigma^*_{(CC)}$] are not significant in either case. Contributions to steric exchange energy, the energy associated with N-electron antisymmetry of the wave function, which is closely related to the concept of steric 'contact' between electron pairs, were evaluated by computing the interactions between occupied

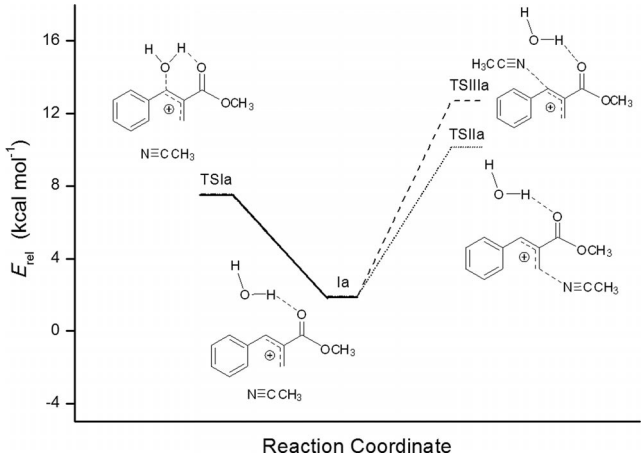


Figure 5. Energy diagram with predicted geometries and relative energies obtained from calculations of the stepwise pathways (dashed line = S_N1 and dotted line = S_N1') for unsubstituted α-methylene-β-hydroxy ester **1a** (R = H).

NLMOs. The investigation of such interactions in both transition state structures, TSIIA and TSIIIA, indicated that only the latter TS presented some steric destabilizing interactions between acetonitrile and water molecules (Figure S17 of the Supporting Information); however, such steric effects can be considered to be of minor significance.

Although in all cases the theoretical and experimental results are consistent with a stepwise process, the hypothesis that the formation of a carbenium ion as a reaction intermediate is the rate-controlling step was puely based on the experimental evidence. Moreover, the stepwise S_N1'-type process ultimately leads to the major acetamides **2**, which have greater stability. This stability is endorsed by comparing the changes in the Gibbs free energies of the products (acetamides **2** and **3**) with those of the reagents (α-methylene-β-hydroxy esters **1**), as shown in Table 4. For all reagents **1**, independent of the substitution pattern (R), the S_N1' path is more exergonic than the S_N1 path.

Table 4. Changes in the calculated Gibbs free energies (kcal mol^{-1}) of acetamides **2** and **3** in relation to those of the reagents (α-methylene-β-hydroxy esters **1**).

1	R	Acetamide **2**	Acetamide **3**
1a	H	–20.37	–16.76
1b	CH_3O	–18.56	–14.37
1f	NO_2	–16.52	–13.76

It can therefore be assumed that nucleophilic substitution involving allylic derivatives bearing aryl moieties is strongly dependent on the nature of the substituent. This effect is directly related to the stabilization of a benzylic carbenium ion intermediate, whereas product formation is controlled kinetically.

Conclusions

Kinetic and theoretical investigations were undertaken to elucidate the mechanism involved in the acid-mediated solvolysis reaction of α-methylene-β-hydroxy esters in acetonitrile to give isomeric acetamides **2** and **3**. The kinetic data showed that the reaction rates are greatly increased by electron-donating substitution at the *para*-position. All results for the solvent kinetic isotope effect, Hammett plot, and Eyring plot support the hypothesis of rapid protonation in a pre-equilibrium step, followed by the formation of a benzylic carbenium ion intermediate and that the product distribution is governed by kinetic control. The theoretical studies corroborated these results, showing that the preferential formation of allylic acetamide **2** over the isomeric acetamide **3** through a stepwise S_N1'-type mechanism is due to a lower energy barrier.

Experimental Section

General Experimental Procedures: See the Supporting Information.

Typical Procedure for the Synthesis of Acetamides 2 and 3: To a stirred solution of α-methylene-β-hydroxy ester **1** (1.0 mmol) in MeCN (3.0 mL) was added 96% H_2SO_4 (2.5 mmol) at 0–5 °C. The reaction was allowed to warm and stirring was continued at 25 °C. After the time given in Table 1, the final mixture was diluted with CH_2Cl_2 and washed with H_2O, satd. $NaHCO_3$, and brine. The organic extract was dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by chromatography (silica gel; hexane/ethyl acetate, 6:4) to give the corresponding mixture of isomeric acetamides **2** and **3** (Table 1). The major isomer **2** could be separated by filtration after crystallizing from CH_2Cl_2 followed by washing of the solid with diethyl ether. Acetamides **2a**, **2c**, and **2e** are known compounds and their IR and NMR (^1H and ^{13}C) spectra were in agreement with reported data.[16,20a,27]

Methyl (*E*)-2-(Acetamidomethyl)-3-(4-methoxyphenyl)-2-propenoate (2b): White solid; m.p. 108.0–110.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3419, 3285, 2956, 2841, 1714, 1636, 1606, 1538, 1514, 1438, 1307, 1261, 1233, 1180 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.97 (s, 3 H), 3.80 (s, 3 H), 4.34 (d, J = 5.6 Hz, 2 H), 6.18 (br s 1 H), 6.91 (d, J = 8.8 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 2 H), 7.72 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (CH_3), 37.0 (CH_2), 52.3 (OCH_3), 55.4 (OCH_3), 114.3 (2× CH), 125.2 (C), 126.6 (C), 131.8 (2× CH), 142.5 (CH), 160.7 (C), 168.7 (C), 169.8 (C) ppm. $C_{14}H_{17}NO_4$ (263.29): calcd. C 63.87, H 6.51, N 5.32; found C 63.77, H 6.87, N 5.09.

Methyl (*E*)-2-(Acetamidomethyl)-3-(4-fluorophenyl)-2-propenoate (2d): White solid; m.p. 156.5–158.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3434, 3260, 3067, 2953, 1706, 1630, 1601, 1552, 1508, 1225 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 3.85 (s, 3 H), 4.32 (d, J = 6.0 Hz, 2 H), 6.16 (br s 1 H), 7.11 (t, J = 8.6 Hz, 2 H), 7.22 (dd, J = 5.2, 8.6 Hz, 2 H), 7.74 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4 (CH_3), 36.8 (CH_2), 52.4 (OCH_3), 116.0 (d, J = 21.4 Hz, 2× CH), 127.6 (C), 130.3 (C), 131.9 (d, J = 8.3 Hz, 2× CH), 141.3 (CH), 163.3 (d, J = 249.2 Hz, 1 C), 168.4 (C), 169.8 (C) ppm. $C_{13}H_{14}FNO_3$ (251.26): calcd. C 62.14, H 5.62, N 5.57; found C 62.33, H 6.05, N 5.77.

Methyl 3-Acetamido-3-(4-fluorophenyl)-2-methylenepropanoate (3d): Colorless oil; obtained as a mixture (90:10) of **3d/2d**. IR (KBr): $\tilde{\nu}_{max}$ = 3286, 3049, 2954, 2853, 1725, 1653, 1511, 1439, 1293, 1226, 1158, 1093 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.05 (s, 3 H), 3.69 (s, 3 H), 5.93 (s, 1 H), 5.97 (d, J = 9.2 Hz, 1 H), 6.36 (s, 1 H), 6.67 (br s, 1 H), 6.99 (t, J = 8.6 Hz, 2 H), 7.22 (dd, J = 5.6,

8.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5 (CH_3), 52.2 (OCH_3), 54.4 (CH), 115.6 (d, J = 21.3 Hz, 2× CH), 127.8 (CH_2), 128.2 (d, J = 8.1 Hz, 2× CH), 135.5 (C), 139.0 (C), 162.2 (d, J = 244.7 Hz, C), 166.3 (C), 169.3 (C) ppm. HRMS (ESI+): m/z calcd. for $C_{13}H_{14}FNO_3$ $[M + Na]^+$ 274.0850; found 274.0852.

Methyl (*E*)-2-(Acetamidomethyl)-3-(4-nitrophenyl)-2-propenoate (2f): White solid; m.p. 129.5–131.0 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3440, 3250, 3073, 1727, 1631, 1515, 1345, 1236, 1205, 1122 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3 H), 3.88 (s, 3 H), 4.27 (d, J = 6.0 Hz, 2 H), 6.19 (br s 1 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.78 (s, 1 H), 8.28 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (CH_3), 36.7 (CH_2), 52.6 (OCH_3), 123.9 (2× CH), 130.5 (2× CH), 131.2 (C), 139.4 (CH), 140.8 (C), 147.8 (C), 167.6 (C), 170.0 (C) ppm. HRMS (ESI+): m/z calcd. for $C_{13}H_{14}N_2O_5$ $[M + Na]^+$ 301.0795; found 301.0795.

Kinetic Measurements: Solvolysis reactions of substrates **1a–e** (0.10 mmol L^{-1}) in the presence of concentrated sulfuric acid were carried out in a quartz cell with 3.0 mL final volume in acetonitrile. All reactions, at 25.0 °C, were monitored by following the increase in absorbance resulting from the release of the corresponding acetamide products with a spectrophotometer fitted with a thermostatted cell holder (Varian Cary 60). Apparent first-order rate constants (k_{app}) were calculated by using a nonlinear least-squares fitting of the absorbance vs. time. Second-order rate constants (k_H) were obtained from the slopes of plots of the apparent first-order rate constants against the concentration of sulfuric acid.

Computational Procedures: All calculations were performed with the Gaussian03 package at the B3LYP/TZVP level of theory. Geometry optimizations and the search for transition states were performed in the gas phase. To find the guess structures to evaluate the transition states (TS), relaxed scans of the reaction pathways of the potential energy surface were performed. The identified saddle points were then optimized as transition states. TS structures were identified by eigenvalue analysis of the eigenvalues of the Hessian matrix, which exhibited a unique imaginary for each TS structure, confirming that all first-order saddle points are local minima on the potential energy surface. On the other hand, reagent complex and intermediate structures were characterized as minima on the potential energy surface, in which no imaginary eigenvalues were observed. The scan approach was employed because the quadratic synchronous transit method, QST2, failed to generate the initial guess structure or to optimize it to a TS. The TS structures obtained were related to the desired regents and products through IRC calculations.

Crystallographic Data: CCDC-904351 (for **2a**) and -904352 (for **2d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures and ^{1}H and ^{13}C NMR spectra for acetamides **2a–f** and **3d**; computational data, including the Cartesian coordinates and imaginary frequencies of transition state structures TSIa, TSIIa, TSIIIa, TSIb, TSIIb, TSIIIb, TSIf, TSIIf, TSIIIf.

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