Addition of Acrylamide to Amino Aldehydes to Generate Non-Baylis-Hillman Adducts. Formation of Novel *N*-Acylhemiaminals

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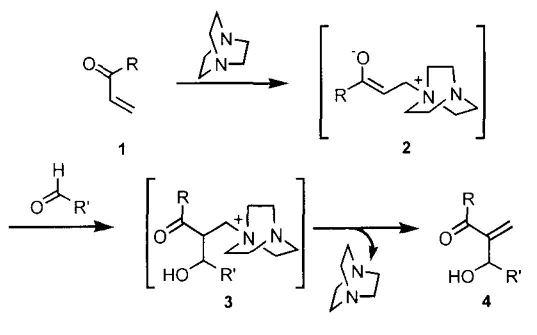
(Received May 6, 1998; CL-980350)

Aldol reactions of chiral aminoaldehydes and methylacrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) produces β-hydroxy methylbutenoates which can be utilized as psuedodipepetides. However, reaction of aminoaldehydes with acrylamide in the presence of DABCO afforded the adducts derived from the addition of the acrylamide nitrogen to the aldehyde to generate *N*-acylhemiaminals. These reactions were found to proceed at a faster rate than the typical Baylis-Hillman reaction and also require the presence of DABCO.

Peptides are responsible for the regulation of countless physiological functions. For these reasons peptides are enticing candidates for drug discovery. However, these molecules are plagued with poor bioavailability and short duration of action. This has spurred the development of new technologies toward the preparation of peptide mimetics in effort to derive structural analogues which do not suffer from short duration of action or lack of oral activity.[1] The peptidomimetic approach has revealed successes in drug discovery programs such as the bradykinin,[2] tachykinin,[3] somatostatin[4] and reverse transcriptase[5] programs, to name a few.

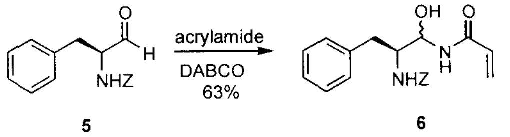
Herein, we report the preparation of a novel series *N*-acylhemiaminals as psuedodipeptides. The synthesis of these peptidomimetics utilizes the Baylis-Hillman protocol for the reaction of chiral aminoaldehydes and acrylates. The Baylis-Hillman reaction has received much attention as an effective method for C-C bond formation.[6] Baylis and Hillman[7] first described this aldol process between α,β-unsaturated esters, ketones, nitriles, and amides and various aldehydes in 1972. Since this time, this base-catalyzed addition of α,β-unsaturated vinyl species to aldehydes has proven to be a rich source of highly functionalized allylic alcohols.[8] These reactions have been proposed[9] to proceed via Michael addition of the cyclic tertiary amine (*i.e.*, DABCO) to the acrylate **1** forming the enolate **2**. The stabilized enolate reacts with the electrophile forming adduct **3** which collapses to product **4** by E2 elimination of the tertiary amine. Reports describing the use of acrylamide as the source of vinyl carbanion in this process are very limited.[7,10] We chose to examine the reaction of acrylamide and aminoaldehydes under Baylis-Hillman conditions to generate chiral butenamides as pseudodipeptides.

Scheme 1.



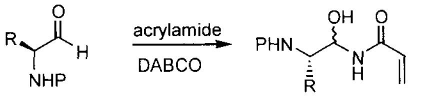
Optimum reaction conditions reported in the literature typically utilize the liquid acrylate as the solvent. In our study, the crystalline acrylamide was solubilised in CH_2Cl_2 and the reaction was performed with DABCO and *N*-protected aminoaldehydes. Attempted Baylis-Hillman reaction of *N*-Cbz-L-Phenylalanal **5** and acrylamide afforded product overnight. Isolation and purification yielded 63% yield of the adduct. ^{1}H NMR, ^{13}CMR, IR and HMBC results indicated that the reaction with acrylamide had yielded a unexpected stable non-Baylis-Hillman adduct. The product was identified as the *N*-acylhemiaminal **6** (scheme 2).

Scheme 2.



The generality of this transformation was explored using a variety of both enantiopure and racemic aminoaldehydes. The aldehydes were prepared using methods described by Castro.[11] The results of this study are summarized in Table 1. The diastereoselectivity[12] was typically 2:1. The major and minor adducts were not characterized.

Table 1. Reactions of aminoaldehydes with acrylamide in the presence of DABCO



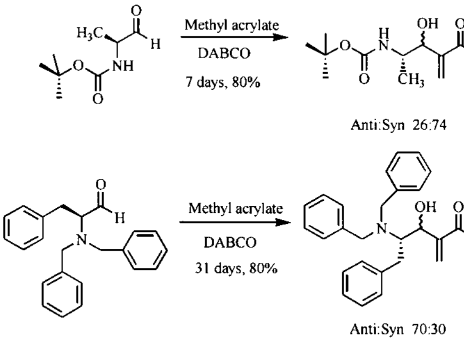
Entry	Aldehyde	Time[a]	Yield[b]
1	*N*-Boc-L-Valinal	13 h	73%
2	*N*-Boc-L-Phenylalanal	18h	63%
3	*N*-Boc-L-Tryptophanal	15h	40%
4	*N*-Boc-L-Prolinal	15h	70%
5	*N*-Boc-L-Serinal(OBn)	15h	29%
6	*N*-Boc-Glycinal	18h	82%
7	*N*-Boc-L-Lysinal(ε-Boc)	18h	48%
8	*N*-Cbz-L-Valinal	15 h	78%
9	*N*-Cbz-Glycinal	14 h	85%
10	*N*-Boc-L-Leucinal	13h	80%

[a] CH_2Cl_2 used as the solvent. [b] Isolated yields.

The formation of the *N*-acylhemiaminal occurs with mild selectivity. Good diastereoselectivity has been observed in the syn diastereoselective formation of β-hydroxy methylbutenoates (scheme 2). In these Baylis-Hillman reactions of mono *N*-protected aminoaldehydes and methyl acrylate, an intramolecular H-bonded Cram model is believed to be responsible for the stereochemical outcome of the enolate addition to the aldehyde.[13,14] These Baylis-Hillman reactions are sluggish and require much longer reaction times in comparison to the preparation of the *N*-acylhemiaminals.

Interestingly, the acrylamide additions only occurs to a small extent (4%) in the absence of DABCO. Under these conditions an obvious solubility issue arises with observation of a

Scheme 3.



nonhomogenous reaction milieu. The ability of DABCO to solublize reaction media has been observed and successfully exploited by other investigators.[15] The formation of the *N*-acylhemiaminals[16] are believed to occur via direct *N*-addition of acrylamide to the aldehyde. A similar addition has been reported in the patent literature for the preparation of acryloamidoglycolates useful in latex polymerization reactions.[17] The products are stable to chromatography conditions and have good shelf lives. The stability of this product may be the result of an intramolecular H-bond network as depicted in Figure 1.

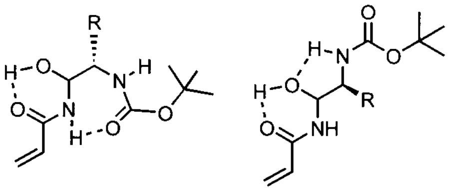


Figure 1. The hemiaminals may be stabilized via an extensive intramolecular hydrogen bonding network.

Further synthetic studies involving these highly functionalized and stable *N*-acylhemiaminals are currently underway. These unique functionalities offer a novel avenue for ensuing acyclic iminium chemistry. In this subsequent study, the formation of the transient iminium species will destroy the hemiaminal asymmetric center thereby eliminating the need to separate or identify the major and minor acrylamide adducts. Application and results of this protocol will be published fully elsewhere.

References and Notes

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12 Diastereomeric ratio was determined by direct examination of ^{1}H NMR of the crude reaction mixture. Ensuing chemistry, *ie.* N-acyliminium ion formations, negate the necessity to separate or identify the major and minor diastereomers. This will be reported in a subsequent full paper.

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16 Typical Experimental: To solution of 9.00 g (31.9 mmol, 1.0 eq.) of *N*-Carbobenzyloxy-2(S)-benzylaminoethanal in 150 mL of methylene chloride (CH_2Cl_2) at room temperature was added 9.07 g (128 mM, 4 eq.) of acrylamide and 3.60 g (31.90 mM, 1 eq.) of 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction was stirred for 18 hours. After diluting with 250 mL of CH_2Cl_2, the mixture was washed with 300 mL of an aqueous 1M citric acid solution and 300 mL of brine. The organics were dried over $MgSO_4$, filtered, and concentrated. Purification by MPLC (1:1, ethyl acetate:hexane) afforded 6.93 g (61.3%) of the hemiaminal as a white solid. Major diastereomer: ^{1}HNMR ($CDCl_3$, 300 MHz): d 7.34-7.24 (m, 10H), 6.19 (dd, 1H, J = 15.8 Hz, 0.5 Hz), 6.01 (dd, 1H, J = 10.4 Hz, 6.8 Hz), 5.64 (dd, 1H, J = 9.9 Hz, 0.5 Hz), 5.25-4.87 (m,4H), 3.11 (dd, 1H, J = 9.5 Hz, 4.7 Hz), 2.94 (dd, 1H, J = 7.6 Hz, 3.0 Hz), Mass Spec (FAB-TGN) (-ions) m/e 337.1 (M-H_2O). Anal. calc'd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.57; H, 6.21; N, 7.70.

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