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CARBOXYL-MODIFIED AMINO ACIDS AND PEPTIDES: I) AN EFFICIENT METHOD FOR THE SYNTHESIS OF MONOFUNCTIONALIZED ENAMINES AND MONOFUNCTIONALIZED METHYL KETONE DERIVATIVES FROM THIOAMIDES VIA EPISULFIDES AND THIOIMINIUM SALTS

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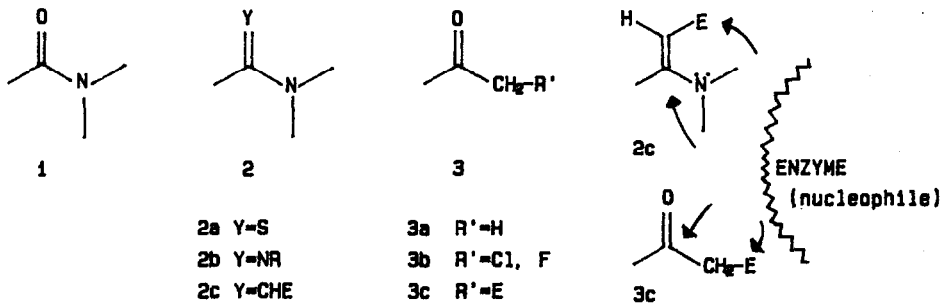
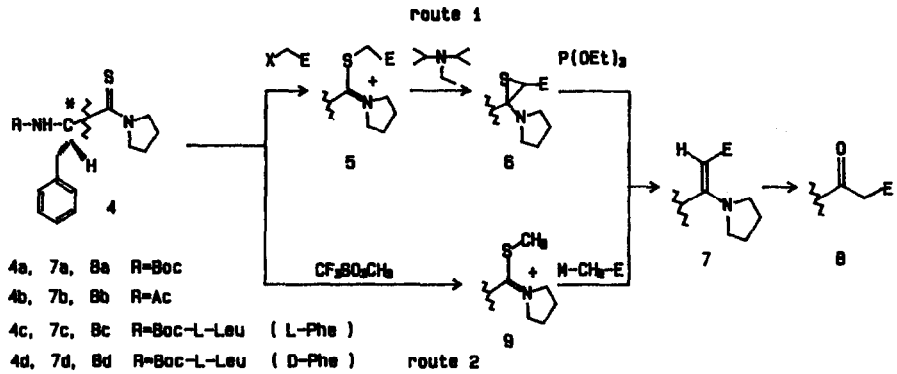
ABSTRACT: Thioamides **4** were transformed by two convenient routes to various functionalized enamines **7** containing different electron-withdrawing groups E which on subsequent hydrolysis gave the corresponding methyl ketone derivatives **8**. Application of this methodology to obtain modified dipeptides at the carboxyl end, the determination of stereochemistry and the degree of racemization are discussed.

Proteolysis is an important biological process[2] and a search for drugs that act as protease inhibitors led to a variety of structural modifications[3] of the peptide bond of the substrates. For example, replacement of the carbonyl oxygen of an amide **1** by sulfur or nitrogen, as in thioamide[4] **2a** or amidoxime[5] **2b** results in less susceptibility to enzymatic hydrolysis and weak competitive inhibition. Changing the nitrogen atom of the amide for a carbon as in the methyl ketone[6] **3a** and halomethyl ketone[7] **3b** also leads to protease inhibition. Here we report the synthesis of two new carboxyl-modified substrates of α-chymotrypsin, enamines **2c** and methyl ketones **3c**, which are isosteric with **2a-b** and **3a-b** and may behave as effective active site inhibitors.



The enamines **2c** were generally prepared from the thioamides according to the Eschenmoser sulfide contraction[8] method. A variety of methylene electrophiles containing a wide range of functionalities were employed. Thus, Boc-thioamide **4a** reacts with active α-halogenated methylene reagents (XCH_2E, Table 1) to form the ∝-thioiminium salt **5** which, after removal of the acidic proton with a base, cyclizes to the episulfide **6** from which sulfur is extruded with a thiophilic reagent yielding a functionalized enamine **7a**. In this way several enamines[9] **7a** (Table 1, entries 1-4,7-10), having different electron-withdrawing groups, were synthesized. However, attempts to extend this procedure to bromonitromethane as the electrophile were unsuccessful.



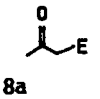
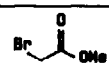
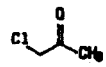
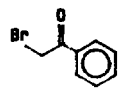
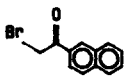
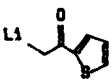
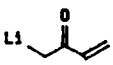
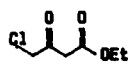
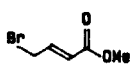
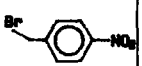
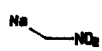
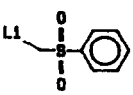
This prompted us to develop an alternate route to obtain the desired nitroenamine **7a**. Thus alkylation of Boc-thioamide **4a** with methyl triflate results in the formation of the electrophilic thioiminium[18] intermediate **9** which in turn reacted with the carbanion of nitromethane to give the corresponding nitroenamine **7a** (entry 11). We extended this procedure to other nucleophiles such as the enolate of 2-acetylthiophene, methyl vinyl ketone, and the anion of methyl phenyl sulfone (entries 5, 6, 12). Also, following the reaction conditions of routes 1 and 2 with N-Ac-thioamide **4b**, the corresponding enamine derivatives **7b** (entries 1-5, 7, 11) that bear analogy to α-chymotrypsin substrates were successfully prepared. Similarly, enamine dipeptide analogues, **7c** and **7d** (E= COC_6H_5, Y=45%; E= COC_4H_3S, Y=19%; E= NO_2, Y=47%) were also prepared from thiodipeptides **4c** and **4d** using these two different procedures. In addition, the methodology described herein is also applicable to the preparation of enamines of other amino acids such as Boc-leucine and Boc-methionine (E= CN, Y=32%; E= NO_2, Y=37%).

Mild acid hydrolysis (silica gel or 0.4N HCl in MeOH) of the enamines **7** yields the desired functionalized methyl ketone derivatives **8** (Table 1: **8a** and **8b**). It should be pointed out that the dipeptide analogues **7c, 7d, 8c, 8d** (E= COC_2H_5; E= COC_6H_3S; E= NO_2) gave no evidence of having suffered any racemization under our reaction conditions as demonstrated by the absence of diastereoisomers (mixtures of which were prepared for comparison purposes) in their ^1H NMR (400 MHz) spectra.

All the enamine analogues showed one set of resonances in their ^1H NMR spectra (400 MHz) in $CDCl_3$. The assignment of the Z-configuration was based on NOE experiments for enamine **7a** (E=CO_2Me) which showed intensity enhancement for the vinylic proton when the CαH was saturated.

The peptide methyl ketone analogue **8a** (E=CN) was also successfully elongated from the amino terminal. Thus following standard reaction conditions, the amino group of **8a** (E=CN) was deprotected (3N HCl in MeOH) and the resulting salt was treated with triethylamine followed by acetylation (Ac_2O) or by coupling with Boc-Leu-OH (DCC, HOBt) to give the β-ketonitrile **8b** (E=CN, Y=31%) or **8c** (E=CN, Y=28%).

Table 1: Synthesis of functionalized enamines and functionalized methyl ketone derivatives of Boc- and N-Ac-phenylalanine[11]

Entry	Reagent 	Route	YIELD[a] (%)			
			Intermediate		Analogues of α-chymotrypsin substrate	
			Boc-Phe		N-Ac-Phe	
			 7a	b  8a	 7b	b  8b
1		1[c]	52[d] (65)	85[e]	25[d] (45)	74[e]
2		1	35[d] (55)	50[e]	21[d] (41)	48[e]
3		1	48[f] (58)	62[g]	43[f] (54)	72[g]
4		1	45 (52)	58	35 (52)	69
5		2[h]	27	54	22	62
6		2[h]	36	55	--[i]	--
7		1[j]	21 (31)	--[k]	16 (26)	--[k]
8		1	22[d] (35)	48[e]	--[k]	--
9		1[j]	36 (65)	83	--[i]	31[l]
10		1	--[m]	50[d] (65)	--[m]	35[d] (50)
11		2[h]	34	--[n]	21	--[n]
12		2[h]	40[d]	85[e]	--[i]	--

A combination of the above pathways provides an easy access to a variety of functionalized enamine and functionalized methyl ketone peptide analogues. This approach has not been previously applied to the synthesis of peptide analogues and it is useful knowledge that the reaction conditions turn out to be compatible with both chiral centers and amide functions. The experimental details and biological results will be reported elsewhere.

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11. **a)** isolated yield; values in parenthesis refer to yields based on the starting material consumed. **b)** by ^{1}H NMR (400 MHz; $CDCl_3$), we observed an AB pattern corresponding to an integration of 2 H for the ketone form (entries 1, 9, 11) and for all other cases a single peak 1 H for the enol form. **c)** unless stated otherwise the temperature and the time of the reaction followed the general procedure of route 1: 1° substrate **4**, XCH_2E, NaI, CH_3CN, 24 hrs, r.t.; 2° diisopropylethylamine, triethylphosphite, 20 hrs, r.t.. **d)** flash chromatography on alumina. **e)** flash chromatography on silica gel catalyzed the hydrolysis of enamines. **f)** unless mentioned flash chromatography is on silica gel. **g)** unless mentioned enamines were hydrolyzed with 0.4N HCl in MeOH. **h)** route 2: 1° substrate **4**, methyl triflate THF, 15 min, 0°C; 2° at -78°C, a mixture of the enolized nucleophile with base in THF, was added, 30 min at -78°C; entries **5** and **6**, base LDA; entry **12**, base n-BuLi; entry **11**, base NaH, enolization and condensation at 0°C. **i)** enamines could not be isolated under the standard procedure. **j)** the reaction with the electrophile is 16 hrs at 65°C after the addition of the base and the thiophile 4 hrs at room temperature and 10 hrs at 65°C. **k)** a mixture of complex products was obtained. **l)** obtained by deblocking the Boc group with 3N HCl in MeOH and acylation with Ac_2O and pyridine. **m)** enamine was too unstable to be isolated and hydrolysis occurred during purification on alumina. **n)** hydrolysis using 0.4N HCl in MeOH afforded R-Phe-OMe.

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