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SYNTHESES OF PROTECTED VINYLIC AMINO ACIDS BY INTERMOLECULAR LEWIS ACID CATALYZED ENE REACTIONS

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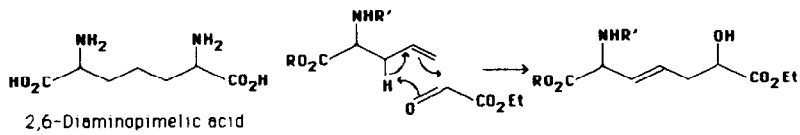
Abstract : Intermolecular ene reaction between ethylglyoxylate and allylic amino acid derivatives gave highly functionalized unsaturated pimelic acids in one step. This synthetic approach appears as a new efficient method for the synthesis of vinylic amino acids.

Vinylic amino acids are biochemically and pharmacologically important molecules [1]. Chemically no direct access to vinylic amino acids is available. For the synthesis of vinylic 2,6-diaminopimelic acid derivatives, part of our antibiotic program, we needed an efficient and rapid method for the synthesis of the seven carbon backbone of pimelic acid containing a double bond. Snider [2] and Achmatowicz [3] described the synthesis of allylic amino acids by the ene-reaction. It appeared to us that if derivatives of allylglycine could react with ethylglyoxylate in an ene-process this would give our desired molecules containing the vinylic amino acid moiety with the E configuration (scheme 1).



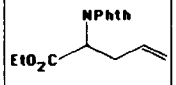
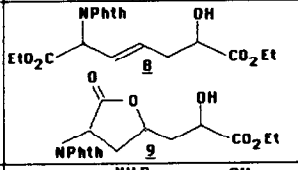
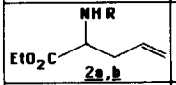
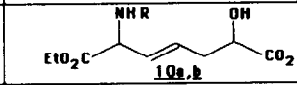
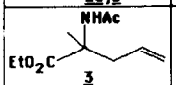
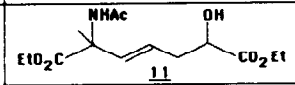
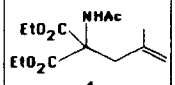
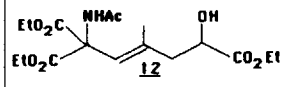
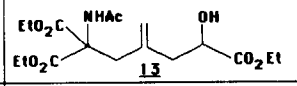
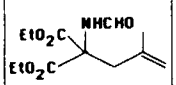
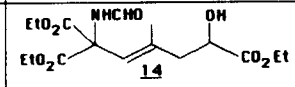
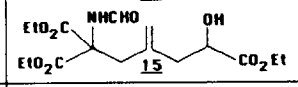
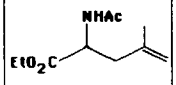
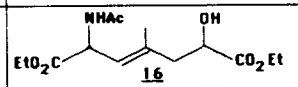
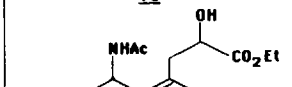
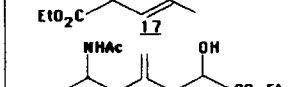
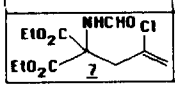
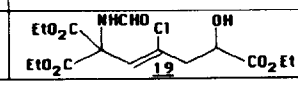
Scheme 1

The ene reaction is a powerful synthetic method for carbon-carbon bond formation [4,5]. To the best of our knowledge no intermolecular ene-reaction with alkenes bearing functionalized substituents in the neighbouring of the allylic hydrogens was described.

The use of allylglycine derivatives as the alkenes in ene reactions to produce protected vinylic amino acid is described in this paper. The application of our method to the synthesis of a series of 2,6-disubstituted unsaturated pimelic acids in one step is also reported.

When reacting 2b with ethylglyoxylate in the condition of Lewis acid catalyzed ene-reaction[6] (1 eq $FeCl_3$, $\leq$ 1 eq ethylglyoxylate, CH_2Cl_2), the desired compound 10b (6 %) was obtained together with unreacted starting olefin 2b. Intermolecular ene reactions are generally performed with an excess of the olefin compared to the enophile : the adduct of the ene-reaction being an olefin can react to give the bis-adduct derivative [7,8]. However with 2

Table 1

Ene (a)	Ene/OHC-COOEt/$FeCl_3$ T°C , Time	Product(s) (a)	Ratio	Yield (b)
 1	1/2/3 -50°, 2h then -20°, 16h	 8 9	4 5	98%
 2a,b	1/2/3 25°, 16h	 10a,b		a: R=$COCF_3$ b: R=Ac 85%
 3	1/2/3 25°, 16h	 11		73%
 4	1/2/4 -10°, 0.5h	 12  13	1 4 (c)	90%
 5	1/2/4 -10°, 0.5h	 14  15	1 3 (c)	75%
 6	1/2/3 25°, 16h	 16  17  18	1 3 2 1	67%
 7	1/2/4 -10°, 0.5h	 19		95%

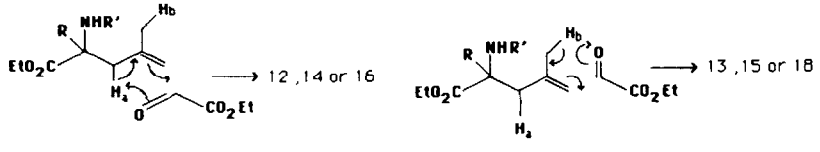
(a)-Racemic compounds and diastereoisomeric mixtures
(b)-Yield of purified isolated compounds (c)-Separated as their O-Mesyl derivatives

General method[12]: $FeCl_3$ was suspended in Vml CH_2Cl_2. Ethylglyoxylate in Vml CH_2Cl_2 was added to the suspension and stirring was continued for 15-30'. The solution was cooled to the indicated temperature or with an ice bath. The alkene in Vml CH_2Cl_2 (final volume 3V giving a 0.25M solution of the ene) was added dropwise with stirring (5-10'). The mixture was stirred for the indicated time and at the indicated temperature, poured in ice and extracted three times with CH_2Cl_2. The organic extract was washed with 1N HCl then brine and dried over $MgSO_4$. The solvent was removed in vacuo and the residue purified by flash silica gel chromatography (ethylacetate-heptane).

equivalents of enophile and an excess of $FeCl_3$ to neutralize the basic carbonyl oxygens of olefine, the desired compound 10b was obtained in a good yield (table 1). Application of these reaction conditions to the allyl amino acid derivatives 1 - 7 provided us with the key intermediates 8 - 19.

As a by-product a lactone could be expected [8] ; this was observed in the reaction with olefin 1. The regioselectivity of the ene-reaction with alkenes that possess non equivalent allylic hydrogens is governed by electronic and steric factors. Under Lewis acid catalysis regio-and stereo-controls of the ene-reaction are known to be mainly governed by electronic factors. However in our examples we were able to control the regioselectivity by steric factors. Olefins 4, 5 and 6 have two sets of allylic hydrogens, Ha and Hb (scheme 2). With a high steric hindrance in the neighbouring of the Ha allylic hydrogens (olefin 4) the regio-isomer 13 was formed selectively. With olefin 5 where steric hindrance is lowered, the regioselectivity ratio was lower. Finally, with olefin 6 where the steric hindrance of the Ha hydrogens is not high enough to control the approach, the regioselectivity ratio was inverted and 16 + 17 were formed selectively. Surprisingly, stereospecificity was lost, the major compound being the Z isomer 17. We have verified that the obtained ratios were not the result of an equilibration process under acidic conditions (in addition the thermodynamically more stable olefins 12 or 14 are not the major products in the ene reactions with 4 and 5). The regioselectivity ratio was not dependent of the reaction conditions (temperature, time and work-up).

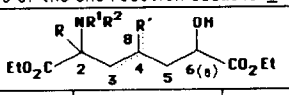
Thus a new application of the intermolecular Lewis acid catalyzed ene-reaction was established. Developpement of this application to the readily accessible optically active alkenes 1, 2 and 6 [9] or the use of chiral esters of glyoxylic acid [10] is a promising route to the synthesis of the stereoisomers of 2,6-disubstituted pimelic acid derivatives. The transformation of alcohols 8 - 19 into 2,6-diaminopimelic acid [11] derivatives and the biological properties of these compounds will be described elsewhere.



Scheme 2

Acknowledgements : We are indebted to Prof. F. LE GOFFIC and Dr. M. LANGLOIS for their constant interest and encouragements.

Table 2 ^{1}H-NMR Chemical shifts of the ene reaction adducts 8-19 (b)



	H-2	H-3	H-4	H-5	H-8
8	5.35,d(1H)	6,m(2x1H)	6,m(2x1H)	2.5,m(2H)	-
9	5.1,broad(1H)	2.4,broad(2x2H)	(a)	2.4,broad(2x2H)	-
10a	5.05,broad(1H)	5.75,m(2x1H)	5.75,m(2x1H)	2.45,m(2H)	-
10b	5.1,d of d(1H)	5.7,m(2x1H)	5.7,m(2x1H)	2.45,m(2H)	-
11	-	5.7,m(2x1H)	5.7,m(2x1H)	2.45,m(2H)	-
12	-	6.3,broad s(1H)	-	2.45,d(2H)	1.65,broad s(3H)
13	-	3.1,m(2H)	-	2.45,broad(2H)	4.9,d(2H)
14	-	6.3,broad s(1H)	-	2.4,broad(2H)	1.65,broad s(3H)
15	-	3.15,broad s(2H)	-	2.4,broad(2H)	4.95,broad d(2H)
16	5.2,m(2x1H)	5.2,m(2x1H)	-	2.5,m(2H)	1.85,s(3H)
17	5.15,m(2x1H)	5.15,m(2x1H)	-	2.7,m(2H)	1.8,s(3H)
18	4.65,broad(1H)	2.55,broad(2x2H)	-	2.55,broad(2x2H)	4.95,broad(2H)
19	-	6.8,broad s(1H)	-	2.85,m(2H)	-

(a)-Masked by the Ethyl CH_2-O quartets ~4.2ppm

(b)-Solvent $CDCl_3$, values in ppm down field from TMS. T60 Varian Spectrometer

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