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REACTIONS OF AN ELECTROPHILIC GLYCINE CATION EQUIVALENT WITH GRIGNARD REAGENTS A SIMPLE SYNTHESIS OF β,γ-UNSATURATED AMINO ACIDS[1]

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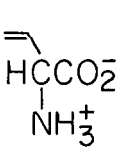
Summary: A simple and general synthesis of α-amino acids employing vinyl and alkyl Grignard reagents with a glycine cation equivalent is described.

β,γ-Unsaturated α-amino acids are natural products that possess antibiotic activity and enzyme inhibitory properties.[3] Several synthetic β,γ-unsaturated α-amino acids have been designed as specific irreversible inhibitors of pyridoxal phosphate dependent enzymes.[4] The parent, vinyl glycine 1, is also a useful chemical intermediate upon which to build novel functionality.[5]

A simple and general synthesis of this class of compounds poses a significant synthetic challenge. The methods of Rapoport[6a] and that of Hanessian[6b] provide optically active 1 by the degradation of methionine (2) and glutamic acid (3), respectively. Other routes furnish racemic materials in widely varying yields. Recently, Fitzner et al.[6c] report that the oxidative rearrangement of γ-phenylseleno-α,β-unsaturated esters affords in some cases good yields of protected β,γ-unsaturated α-amino acids.



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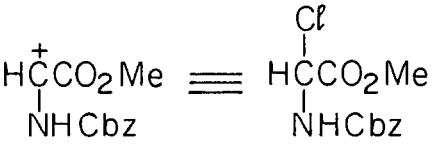

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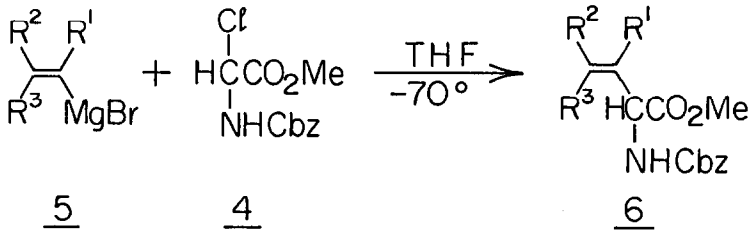
We describe a new approach to β,γ-unsaturated α-amino acids which involves the condensation of an electrophilic glycine cation equivalent 4 with organomagnesium reagents.[7] Reaction of a vinyl Grignard reagent 5 with N-benzyloxycarbonyl α-chloro glycine methyl ester 4,[8] gives the target amino acid derivative 6 in yields of 55 to 65% (table).

Typically a vinylic Grignard is prepared in THF and then added to a solution of 4 (0.45 equivalents) in THF at -70°. Two hours later, the reaction is quenched with 1.0 N citric



5 4 6

acid. Work up of the reaction mixture and purification by chromatography on silica gel gives the protected α-amino acid derivative 6.[9] Hydrolysis of the latter gives the β,γ-unsaturated α-amino acid. α,β-Unsaturated amino acid derivatives isomeric with 6 or products resulting from Grignard attack at the ester or carbamate moieties are not detected.[10] The treatment of the ether, N-Cbz-α-methoxy-Gly-OMe, 7, with vinyl magnesium bromide does not produce 6, even upon warming the reaction mixture to 0°C.

The reaction of vinyl magnesium bromide and N-Cbz-L-Phe-α-chloro-Gly-OMe[11] does not result in asymmetric induction, but leads to a 1:1 ratio of diastereomeric esters 11 as determined by ^{13}C NMR spectroscopy and HPLC.

Our method for functionalizing glycine at the α-position through electrophilic cation equivalents appears to be quite general. For example, proceeding in the same manner as with 5, cyclohexyl, cyclopropyl and 3-butenyl magnesium bromide react with 4 to give N-Cbz-α-cyclohexyl-Gly-OMe (60%), N-Cbz-α-cyclopropyl-Gly-OMe (35%), and N-Cbz-α-(but-3-en-1-yl)-Gly-OMe (46%) respectively. A particularly useful application is the reaction of the trifluorovinyl magnesium bromide with 4, which gives a very high yield of the trifluorovinyl derivative 14, (see table).

There are relatively few examples of amino acid syntheses which involve the reaction of carbon nucleophiles with cationic amino acid synthons.[12] O'Donnell's syntheses of aryl substituted amino acids, as well as amino acids containing a β-tertiary carbon, from the condensation of nucleophiles with $Ph_2C{:}NCH(OAc)CO_2Et$[13] are noteworthy. Our work expands the utility of the cationic glycine unit 4 to embrace a straightforward and high yield synthesis of β,γ-unsaturated α-amino acids.

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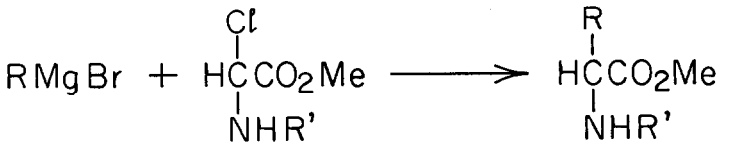
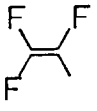
TABLE:



R	R'	Product	Yield[b,e]
 [a]	Cbz	8	65%
	"	9	56%
 [c]	"	10	60%
 [d]	Cbz-L-Phe[f]	11	60%
	Cbz	12	60%
	"	13	65%
	"	14[g]	85%

(a) Available from Aldrich Chemical Co. (b) Refers to isolated (non-optimized) yields of chromatographically pure products. (c) The reagent was obtained from a mixture of cis and trans-2-bromo-2-butene (Aldrich). (d) Inferior yields resulted when three equivalents were employed. (e) About 10-20% of N-Cbz-α-hydroxy-Gly-OMe is usually recovered. (f) In our hands, pyrolysis of N-benzyloxycarbonyl-L-phenylalanyl-2-amino-4-(methylsulfinyl) butyric acid methyl ester at 150-170°[6a], led to (E+Z)-N-benzyloxycarbonyl-phenylalanyl-2,3-dehydro-2-aminobutyric acid methyl ester. (g) IR (neat): 3320, 1798 , 1760, 1720 cm^{-1}. ^1H NMR (80 MHz, $CDCl_3$): δ 3.84 (s, 3H, OMe), 5.23 (broad dd, 1H, J = 7.8, 28 Hz, CH), 5.73 (broad d, 1H, J = 7.8 Hz, NH), 5.15 (s, 2H, CH_2Ph), 7.36 ppm (s, 5H, Ph). ^{19}F NMR (75 MHz, $CDCl_3$): δ -100.4 (dd, F_a, J_{ab}^{gem} = 72 Hz; J_{ac}^{cis} = 34 Hz), -118.5 (dd, F_b, J_{ba}^{gem} = 72 Hz, J_{bc}^{trans} = 116 Hz), -185.9 (ddd, F_c, J_{ca}^{cis} = 34 Hz, J_{cb}^{trans} = 116 Hz, J_{c-H_α} = 28 Hz).

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