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SYNTHESIS OF KETOMETHYLENE ANALOGS OF DIPEPTIDES

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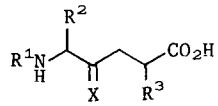
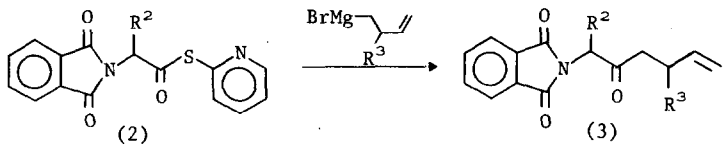
Summary: A convenient method of synthesizing ketomethylene dipeptides by using homoallylic Grignard reagents as amino acid analog synthons is described.

In the course of our studies concerning the synthesis of orally active peptide analog antihypertensive agents,[1] we desired a convenient general route to a variety of ketomethylene dipeptides (1, X=O).



(1)

We wish to report here a successful general method based on the reaction of 2-pyridyl-thioesters of N-phthaloyl-L-amino acids (2) with homoallylic Grignard reagents. This gives the ketones (3), as expected by analogy with literature precedent.[1,2]

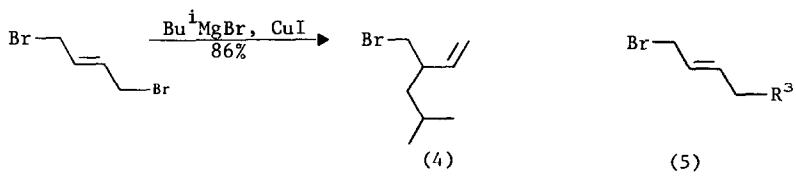


(2) (3)

Table 1. Preparation of Ketones (3)

R^2	R^3	Equivalents of Magnesium and Alkyl Bromide	% yield of (3) from (2)
CH_2Ph	H	2.5	53
CH_2Ph	Me	3.0	49
Bu^t	Bu^t	5.0	57

The Grignard reagents, prepared from the corresponding bromide, magnesium turnings, and dry diethyl ether in the usual way, were added to the thioesters (2) in dry tetrahydrofuran under nitrogen at 0°C. The bromide (4) was prepared in 86% yield from 1,4-dibromo-2-butene and isobutyl magnesium bromide in the presence of 1 mole % cuprous iodide. The procedure differs from that of Mesnard and Miginiac[3] only in that they omitted the cuprous iodide. In our hands their procedure gave not the desired S_N2' product, but predominantly the S_N2 product (5, R^3 = Me, Pr^i, Bu^i).



(4) (5)

The ketones (3) were ketalised with 2-methoxy-1,3-dioxolane and p-toluenesulphonic acid in methanol (6 days reflux)[4] and the phthalimido protecting group was removed by treatment with

hydrazine in ethanol (overnight reflux). The amines were then acylated with a variety of acid chlorides in pyridine.

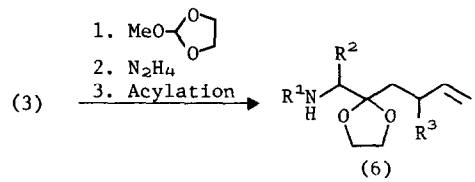


Table 2. Preparation of Ketals (6)

R^1	R^2	R^3	% yield of (6) from (3)
PhCO	CH_2Ph	H	50
PhCO	CH_2Ph	Me	41
$PhCH_2OCO$	Bu^i	Bu^i	59
Cl_3CCH_2OCO	Bu^i	Bu^i	80

Two methods were found effective for cleavage and oxidation of the terminal olefin to a carboxylic acid.

I Ozonolysis at -78° in dry dichloromethane, then treatment with triphenylphosphine (2 equivalents) in ethanol at room temperature for 3 days,[5] followed by evaporation *in vacuo* and Jones oxidation. Direct oxidative treatments of the ozonide were unsatisfactory.

II Treatment with sodium periodate in aqueous acetone with ruthenium tetroxide catalysis.[6]

In some cases the ketal was removed prior to oxidation by treatment with trifluoroacetic acid/water (9:1).

Table 3. Preparation of ketomethylene dipeptides (1)

R^1	R^2	R^3	X	Method of oxidation	% yield of (1) from (6)
PhCO	CH_2Ph	H	O	II	61
PhCO	CH_2Ph	Me	O	I	63
$PhCH_2OCO$	Bu^i	Bu^i	O O	II	33
Cl_3CCH_2OCO	Bu^i	Bu^i	O	II	43

The protected dipeptide analogs (1) could be incorporated in larger peptides by standard peptide coupling techniques.

All isolated compounds exhibited statisfactory spectral data including elemental analysis and/or high resolution mass spectrum.

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