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NEW SYNTHESIS OF DEHYDRODIPEPTIDES FROM SUBSTITUTED OXAMIC ACIDS

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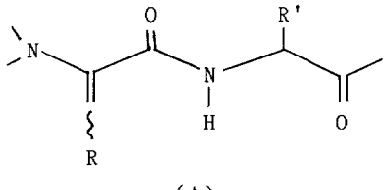
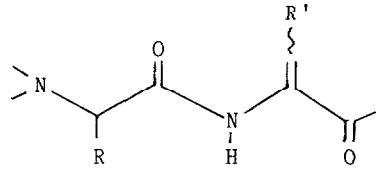
Summary - The condensation of phosphorus ylids with t-butyl oxamic esters derived from aminonitriles gives 2-aza 1,3-dienes ; subsequent reaction with hydrobromic acid provides protected dehydrodipeptides.

Various studies (1) have shown the correlation between the structure and the biological activity of dehydropeptides containing one or more dehydroamino-acid residues such as tentoxin (1) or alternariolide (2).
The direct coupling of an α-dehydroaminoacid with another α-aminoacid is a convenient method for the synthesis of derivatives (A) ; in contrast , it revealed more difficult for derivatives (B) because of instability of the starting material.



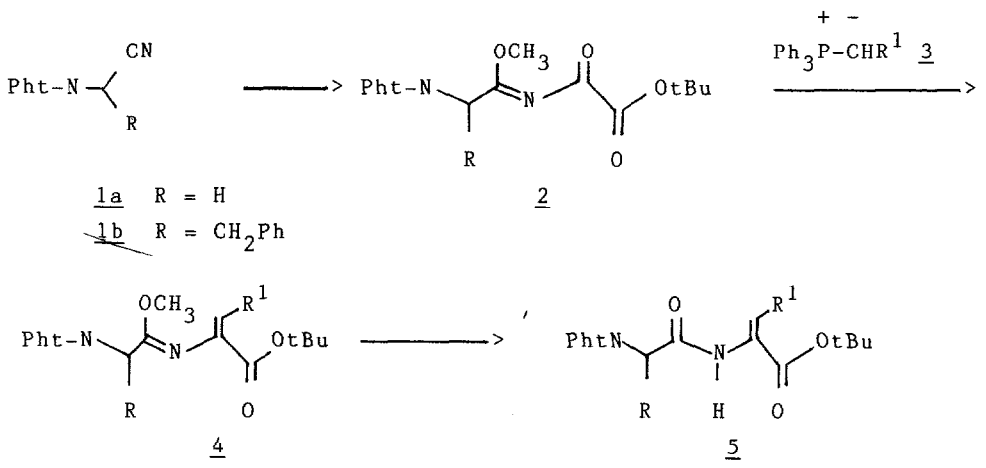
(A)



(B)

The only convenient route consists in the condensation of a ketoacid with a protected α-aminoacid (3).

We have previously reported (4) that protected α-dehydro α-amino-acids were readily accessible from t-butyl oxamic esters . We have now found that this procedure could be adapted to a novel synthesis of dehydrodipeptides .



The α-phtalimidonitriles 1 have been readily prepared from α-chloroacetonitrile (5) 1a or α-phtalimido α-phenylpropionamide (6) 1b . The α-phtalimidonitrile 1 , upon treatment with methanol in the presence of HCl at 0°C (7) then with t-butoxalylchloride at 0°C (8) in the presence of triethylamine, gives good yields of 2 .

We examined the reaction of 2 with non-stabilized ($R^1 = CH_3$) , semi-stabilized (R^1 = Ph) and stabilized ($R^1 = CO_2Me$) ylids 3 . The former gives rise to the expected azadiene but in only a very low yield. In contrast, less basic ylids lead to 4 in 60-70% yields.

Action of a molar amount of gaseous hydrobromic acid (9) gives protected dehydrodipeptides 5 (65-85% yield) (table) .

A typical procedure is as follows :

1 equ. of acyliminoether 2 was added to a stirred solution of 1 equ. of ylid 3 (10) in dry toluene. Upon completion of the reaction (4h under reflux for semi-stabilized ylid and 12h under reflux for stabilized ylid) , the solvent was evaporated and the azadiene 4 separated from triphenylphosphine oxide with hexane.

Transformation of 4 to 5 was obtained by adding 1 equ. of gaseous hydrogen bromide to a solution of 4 in dry toluene, at room temperature.

Yields of 5 are for pure products obtained by recristallization . Compounds 5 were characterized by IR and ^1H NMR and gave satisfactory elemental analyses.

Table - Compounds 2, 4 and 5 prepared

Compound	R	R^1	yield (%)	m.p (°C)	^1H NMR (ppm)[a]
2a	H	-	80	118 (hexane/toluene)	-
2b	$C_6H_5CH_2$	-	98	oil[b]	-
4a	H	C_6H_5	70	oil[b]	7.00(d)
4b	H	CO_2Me	60	119 (EtOH)	6.10
4c	$C_6H_5CH_2$	C_6H_5	60	124 (hexane)	6.70
4d	$C_6H_5CH_2$	CO_2Me	65	oil[b]	5.98
5a	H	C_6H_5	60	258-260 (EtOH)	(c)
5b	H	CO_2Me	85	158 (EtOH)	5.60
5c	$C_6H_5CH_2$	C_6H_5	65	217 (CH_3CO_2Et)	7.30
5d	$C_6H_5CH_2$	CO_2Me	60	126 (EtOH)	5.55

(a) - in $CDCl_3$, olefinic proton (60 MHz)
(b) - crude product directly utilized
(c) - masked by aromatic protons
(d) - presence of another ethylenic signal at 6.38 ppm.

^{13}C NMR analysis of compounds 5 indicates in all cases , only one stereoisomer of Z configuration.
The optical purity of dehydrodipeptides 5c and 5d was determined by measuring optical rotations of phenylalanine obtained after hydrolysis (6N HCl, 12h under reflux)

In the two cases , the compound 5 is optically active but optical purity is only 32% (5c) and 35% (5d). The racemization occurring , may be due to the basic character of the ylid; accordingly it seems difficult to avoid it .

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10- The benzylidenetriphenylphosphorane 3a was prepared from benzyltriphenylphosphonium bromide and t-BuOK; the carbomethoxymethylenetriphenylphosphorane 3b is commercially available.

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