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REGIO- AND STEREOSPECIFIC SYNTHESIS OF N-ALLYL AMIDES BY THE HORNER-WITTIG REACTION

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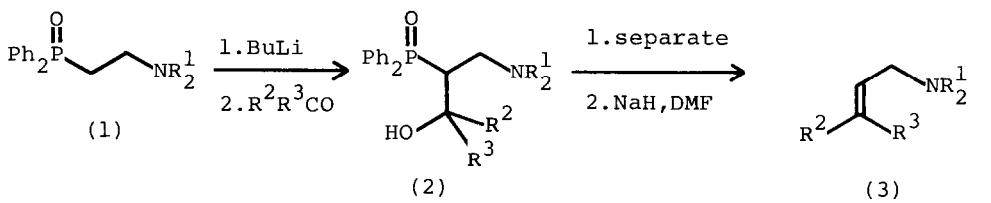
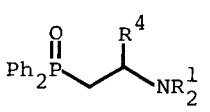
E and Z allyl amides are formed with full regio- and stereochemical control from dianions of β-(acylamino) alkylphosphine oxides by the Horner-Wittig reaction.

Allylic amines (3) can be synthesised[1] regio- and stereospecifically by the Horner-Wittig reaction from (1) since the diastereoisomers of (2) can be separated and elimination of $Ph_2PO_2^-$ is stereospecific.[2] Attempts to extend this route to the more challenging regiochemistry of (5) or (7) failed because anions of (4) did not add to aldehydes or ketones whilst (6) could not be prepared by amine addition to allyl or vinyl phosphine oxides.[3] We now report that amides with the substitution pattern of (5) and (7) can be made by the Horner-Wittig reaction.



(1) (2) (3)



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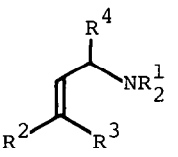

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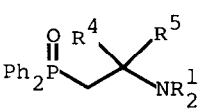

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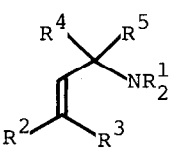
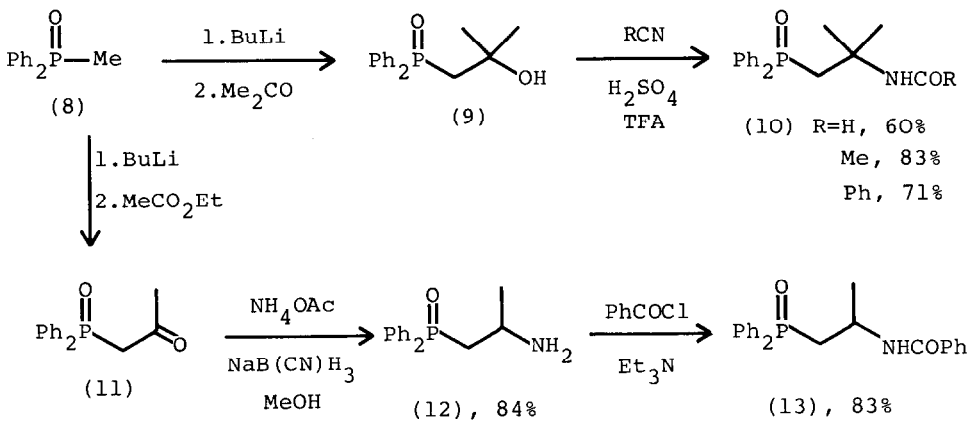


(7)

The starting materials (10) and (13) may be assembled from phosphine oxide (8). The tertiary alcohol (9) gives amides (10) directly by the Ritter reaction.[4] Ketone (11), made by acylation[5] of (8), gives (13) by reductive amination[6] and acylation.



Treatment[7] of amides (10, R=Ph) and (13) with two equivalents of BuLi in LiBr/THF at - 30°C gave red solutions of dianions (14) and (17). These were cooled to - 78°C and one equivalent of an aldehyde or ketone added to give alcohols (15) and (18) in good yield (tables 1 and 2).

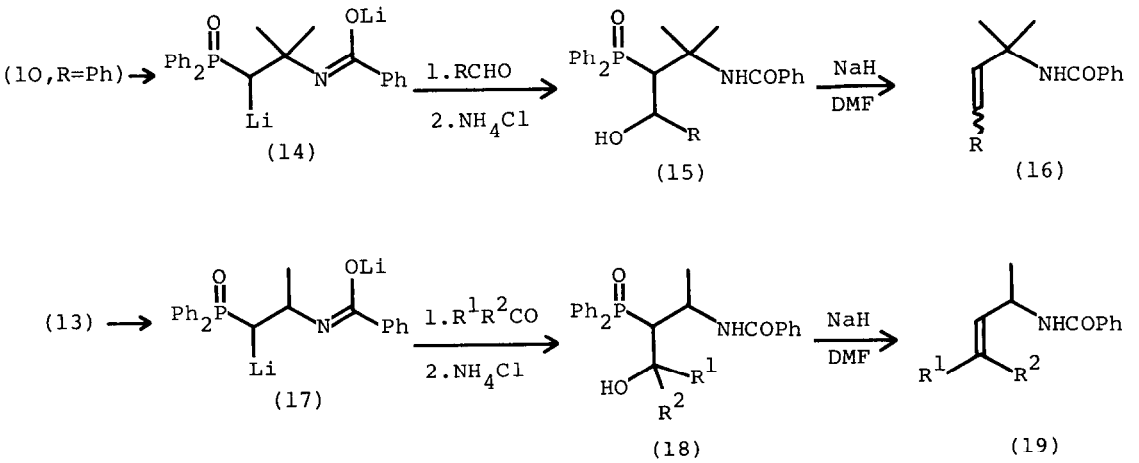


TABLE I : SYNTHESIS OF AMIDES (16)

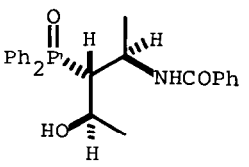
Entry	R	Alcohol (15) yield (stereochem.)[8]	Amide (16) yield (stereochem.)[8]
1	Ph	80 (threo)	84 (E)
2	Me	72 (mixed)	82 (E + Z)
3	i-Pr	47 (threo)	84 (E)
		13 (erythro)	84 (Z)

TABLE 2 : SYNTHESIS OF AMIDES (19)

Entry	R^1	R^2	Alcohol (17) yield (stereochem.)[8]	Amide (19) yield (stereochem.)[8]
1	Me	Me	65	80
2	$-(CH_2)_5-$		61	73
3	Me	H	37.5 (erythro)	82 (Z)
			30.5 (threo)	76 (E)

Alcohols (15) and (18) were separated into pure diastereoisomers by chromatography or crystallisation, except for (15, R=Me) which could not be separated. Elimination of $Ph_2PO_2^-$ was not adversely affected by the amide group and occurred under milder conditions than for (2) (one equivalent NaH, DMF, 20°C, 2 - 4 h.) to give (16) and (19) stereospecifically.

The formation of (15) is highly threo selective whereas the formation of (2) is not stereoselective[1] and simple alkyl phosphine oxides are erythro selective.[2] In the series (13) to (19), stereochemical control over the extra chiral centre (CHMe next to nitrogen) is complete. Only one diastereoisomer is formed on additions to symmetrical ketones (entries 1 and 2, table 2) and only two on addition to acetaldehyde (entry 3). An X-ray crystal structure[9] of the threo isomer of (18, R^1 = Me, R^2 = H) shows that it has structure (20). These stereoselectivities are clearly a consequence of dianion involvement and will be discussed elsewhere.



(20)

These two routes provide access to a range of allyl amides with complementary regiochemistry : the products of table 1, entry 2 and table 2 entry 1 have formally [1,3] transposed structures.

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References

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6. J. M. Varlet, N. Collignon, and P. Savignac, Synth. Commun., 1978, 8, 335.
7. Absolutely dry conditions are essential for dianion formation : the permanent red colour of the dianion should appear soon after one equivalent of BuLi has been added. If much more is needed, the final yield will be poor.
8. The stereochemistry of (16) and (19) was established by NMR using coupling constants for (16) and n.O.e. experiments for (19). The stereochemistry of (15) and (17) was deduced from (16) and (19) since X-ray structure (20) establishes a syn elimination
9. D. Cavalla, W. B. T. Cruse, O. Kennard,and S. Warren, unpublished observations.

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