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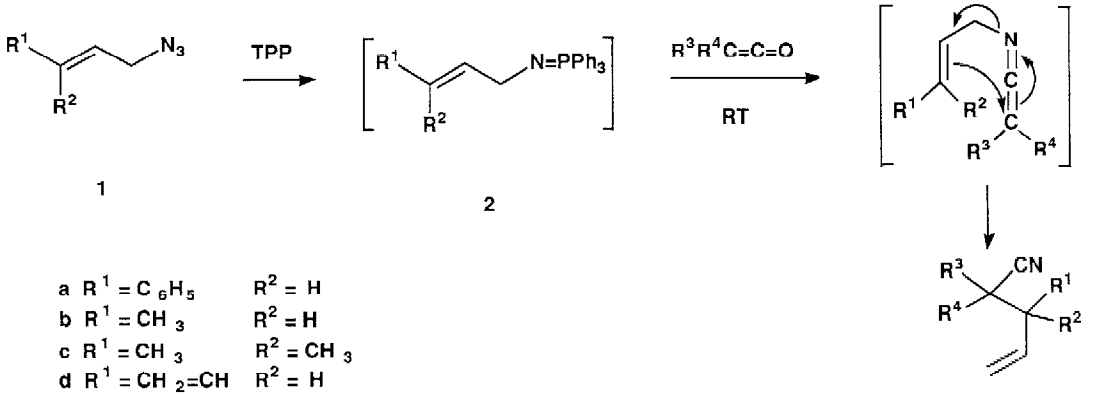
IMINOPHOSPHORANE-MEDIATED ONE-POT CONVERSION OF ALLYL AZIDES INTO α-ALLYLATED NITRILES BY A CONSECUTIVE STAUDINGER REACTION/ AZA-WITTIG REACTION/3-AZA-CLAISEN REARRANGEMENT PROCESS

Pedro Molina*, Mateo Alajarin*, Carmen Lopez-Leonardo
Departamento de Quimica Organica, Facultad de Ciencias, Universidad de Murcia,
Campus de Espinardo, 30071 Murcia, Spain.

Abstract: *One-pot conversion of allyl azides **1** into nitriles **3** under mild and neutral conditions is reported The method involves sequential treatment of **1** with triphenylphosphine and the corresponding ketene to give **3***

The combination of a sequence of individual synthetic methods often has a value in synthesis significantly greater than the sum of the individual reactions. Corey[1] has termed such a sequence a tactical combination. In the last year we have been developing novel approaches to unsaturated heterocumulenes and electrocyclization processes[2]. A very recent report of M. A Walters et al [3] prompted us to disclose our own results on iminophosphoranes derived from allyl azides as well as its application in aza Wittig-type reactions We report herein the iminophosphorane-mediated one-pot conversion of allyl azides into α-allylated nitriles based on the strategy shown in the Scheme

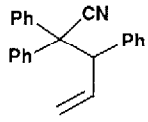
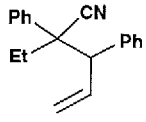
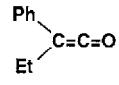
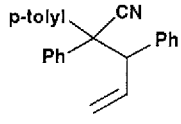
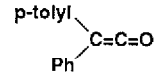
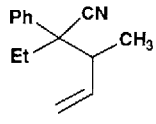
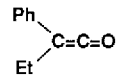
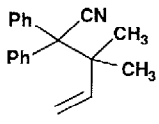
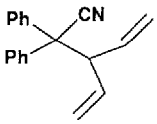
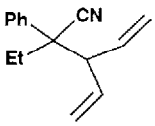
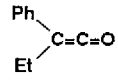
The starting azides **1a**[4], **1b**[5], **1c**[6] and **1d**[7] were prepared from the corresponding bromides and Amberlite IR-400 (N_3^- form)[8]. Staudinger reaction[9] of azides **1**[10] with triphenylphosphine (TPP) in dry benzene led to the corresponding iminophosphoranes which were used without purification for the next step. Aza-Wittig-type reaction of iminophosphoranes with disubstituted ketenes[11] in the same solvent at room temperature for a short period of time leads to the corresponding nitriles **3** in moderate yields[12].



1 2

a $R^1 = C_6H_5$ $R^2 = H$
b $R^1 = CH_3$ $R^2 = H$
c $R^1 = CH_3$ $R^2 = CH_3$
d $R^1 = CH_2{=}CH$ $R^2 = H$

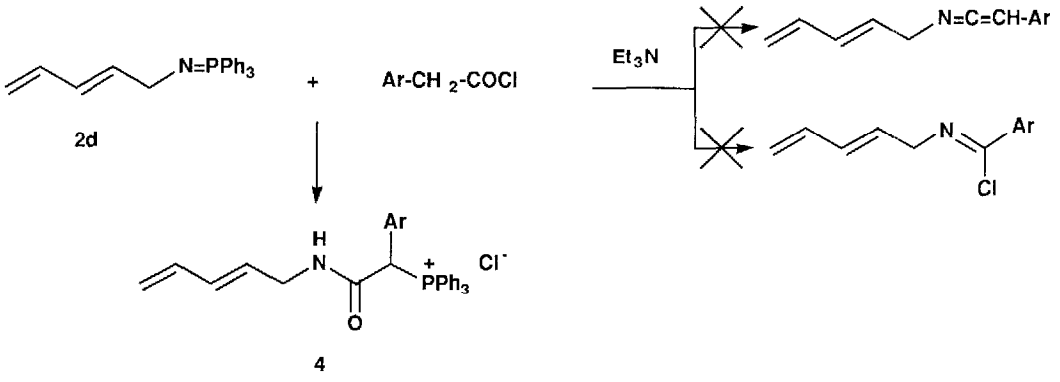
Scheme 3

Entry	Compound 3	Azide	Ketene	Yield (%)
a		1a	$Ph_2C=C=O$	51
b		1a		48
c		1a		44
d		1b		55
e		1c	$Ph_2C=C=O$	47
f		1d	$Ph_2C=C=O$	60
g		1d		41

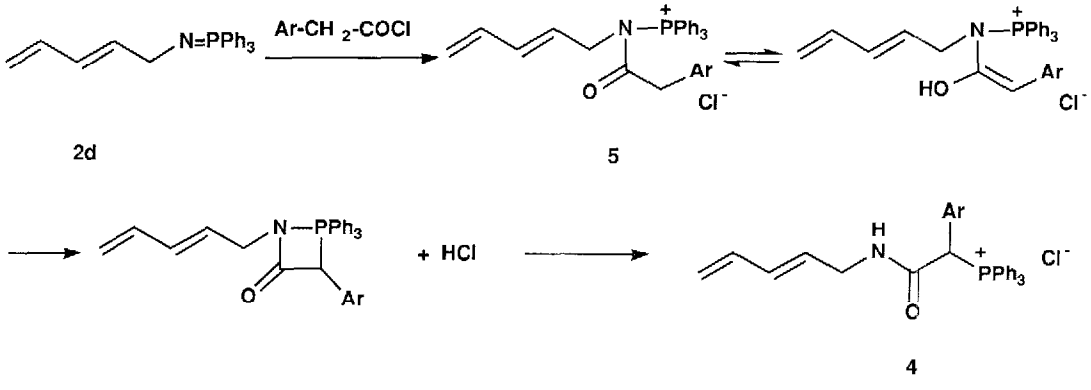
Presumably, the conversion **2** → **3** involves initial formation of a ketenimine as highly reactive intermediate which cleanly undergoes a 3-aza-Claisen rearrangement to give **3**. Formulation of a ketenimine as intermediate is derived from the fact that iminophosphoranes react with ketenes to give ketenimines [13], and is in accordance with a previous report on the preparation of 4-pentenenitriles[14]

A final word about the diastereoselection of this reaction is relevant. Nitrile **3b** was obtained in 48% yield as a 1.6:1 mixture of diastereomers (by ^{1}H NMR); similarly nitrile **3d** was obtained in 55% yield as a 3 7 1 mixture of diastereomers, whereas in the formation of **3c** diastereoselection was not observed

Finally, we have studied the reaction of the iminophosphorane derived from azide **1d** with arylacetyl chlorides in the presence of triethylamine. At first, it was reasonable to expect that iminophosphorane **2d** would react in an aza Wittig-type fashion either with the in situ formed ketene to give a ketenimine or directly with the acyl chloride to give the corresponding imidoyl chloride, however, the reaction unexpectedly led to the formation of compounds **4**[15] It is worth noting that in absence of triethylamine the yields are higher than with triethylamine.



A tentative mechanism for the formation of **4** can be rationalized in terms of an initial acylation to give an acylamino phosphonium salt **5**[16] which undergoes cyclization to give a four-membered ring and further P-N bond cleavage by the action of hydrogen chloride to give **4.**



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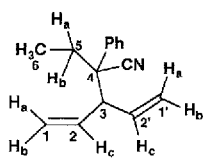
10 Allyl azides are known to equilibrate rapidly at room temperature by 1,3-rearrangement (Gagneux, A , Winstein, S , Young, W G , *J Am. Chem. Soc* **1960**, 82, 5956) The purity of azides **1** used in this work ranged from 60% (**1b**) to ≥ 95% (**1d**) as determined by ^{1}H NMR

11 Disubstituted ketenes were prepared by dehydrochlorination of the corresponding 2,2-disubstituted acyl chlorides with triethylamine (Brady, W T , Dorsey, E D , Parry, F H , *J Org. Chem.* **1969**, 34, 2846)

12. General Procedure To a solution of triphenylphosphine (3 77 g, 1 mmol) in dry benzene (20 ml) was added dropwise a solution of the appropriate azide **1** (1 mmol) in the same solvent and the reaction mixture was stirred at 70°C for 1 h The solution was cooled at room temperature and the ketene (1 mmol) was added under nitrogen The resultant solution was stirred at room temperature for 15 min, then the solvent was removed and the residual material was extracted with n-hexane (2 x 20 ml) The extracts were combined and concentrated to dryness, the crude product was chromatographed on silica gel column, eluting with n-hexane/ethyl acetate (9 1) to afford **3**



Compound **3g** (41%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 0 82 (t, 3H, J = 7 4 Hz, CH_3), 1 91 (dq, 1H, J = 7 4, 13 4 Hz, H_a-5), 2 18 (dq, 1H, J = 7 4, 13.4 Hz, H_b-5), 3 16 (dd, 1H, J = 7 4, 9 0 Hz, H-3), 4 92 (dd, 1H, J = 1 6, 16 8 Hz, H_a-1), 4 97 (dd, 1H, J = 1 6, 10 3 Hz, H_b-1), 5 22 (dd, 1H, J = 1 6, 17 0 Hz, H_a-1'), 5 28 (dd, 1H, J = 1 6, 10 4 Hz, H_b-1'), 5 58 (ddd, 1H, J = 7 4, 10 4, 17 0 Hz, H_c-2'), 5 93 (ddd, 1H, J = 9 0, 10 3, 16 8 Hz, H_c-2), 7 24-7 39 (m, 5H, aryl) ^{13}C NMR (50 MHz, $CDCl_3$) δ 9 52 (CH_3), 31 44 (C_5), 52 48 (C_4), 57 38 (C_3), 118 19* (C_1), 119 0* ($C_{1'}$), 121 01 (CN), 126 93 (C_o), 127 74 (C_p), 128 65 (C_m), 135 18* (C_2), 135 59* (C_2), 136 45 (C_i) *Interchangeables

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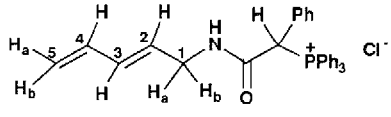
15 Compound **4** (Ar = C_6H_5) (66%) ^{1}H NMR (200 MHz, $CDCl_3$) δ 3 66 (ddd, 1H, J = 5 2, 6 2, 15 4 Hz, H_a-1), 3 84 (ddd, 1H, J = 6 0, 6 1, 15.4 Hz, H_b-1), 4 96 (dd, 1H, J = 1.7, 4 7 Hz, H_a-5), 5 03 (dd, 1H, J = 1 7, 12 2 Hz, H_b-5), 5 47 (ddd, 1H, J = 6 0, 6 2, 15 4 Hz, H-2), 5 93-6 26 (m, 2H, H-3 + H-4), 7 06-7 70 (m, 20H, aryl), 8 00 (d, 1H, J = 12 5 Hz, HC-P), 10 00 (dd, 1H, J = 5 2, 6 1 Hz, NH) ^{13}C NMR (50 MHz, $CDCl_3$) δ 41 17 (C_1), 47 88 (CH, ^{1}J = 51 2 Hz), 116 78 (C_8), 118 10 ($C_{1'}$, ^{1}J = 85 4 Hz), 128 55 (C_i, ^{2}J = 7 0 Hz), 128 64 (C_m, ^{4}J = 1 2 Hz), 128 69 (C_2), 128 98 (C_p, ^{5}J = 3 3 Hz), 129 73 (C_m, ^{3}J = 12 7 Hz), 130 99 (C_o, ^{3}J = 6 1 Hz), 132 24 (C_3), 134 54 (C_p, ^{4}J = 4 5 Hz), 134 64 (C_o, ^{2}J = 9 8 Hz), 136 23 (C_4), 166 7 (CO, ^{2}J = 2 0 Hz) ^{31}P NMR (125 5 MHz, $CDCl_3$) δ 24 23



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