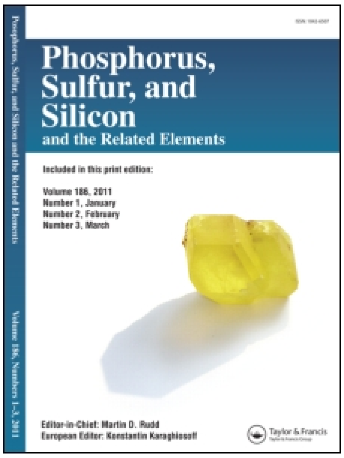


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthetic Applications of β-Functionalized Phosphorus Compounds. An Effective Strategy for the Preparation of Acyclic and Heterocyclic Compounds Derived from Amines and Hydrazones.

Francisco Palacios; Domitila Aparicio; Jesus M. De Los Santos; Jesus Garcia; Encina Rodriguez

To cite this Article Palacios, Francisco , Aparicio, Domitila , Santos, Jesus M. De Los , Garcia, Jesus and Rodriguez, Encina(1996) 'Synthetic Applications of β-Functionalized Phosphorus Compounds. An Effective Strategy for the Preparation of Acyclic and Heterocyclic Compounds Derived from Amines and Hydrazones.', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 401 — 404

To link to this Article: DOI: 10.1080/10426509608545175

URL: http://dx.doi.org/10.1080/10426509608545175

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 401–404
Reprints available directly from the publisher
Photocopying permitted by license only

SYNTHETIC APPLICATIONS OF β-FUNCTIONALIZED PHOSPHORUS COMPOUNDS. AN EFFECTIVE STRATEGY FOR THE PREPARATION OF ACYCLIC AND HETEROCYCLIC COMPOUNDS DERIVED FROM AMINES AND HYDRAZONES.

FRANCISCO PALACIOS*, DOMITILA APARICIO, JESUS M. DE LOS SANTOS, JESUS GARCIA, ENCINA RODRIGUEZ
Departamento de Química Orgánica. Facultad de Farmacia. Universidad del País Vasco. Apartado 450. 01080 Vitoria. SPAIN.

Abstract Enamines **3'A** were very easily prepared in high yield through the addition of achiral and chiral amines **1A** to propargylphosphonium salts, phosphine oxide and phosphonate allenes **2**. β-Functionalized phosphonium salts, phosphine oxides and phosphonates were used for the synthesis of β-amino phosphorus compounds **4A** and for the synthesis of homologation reagents of imines for the preparation of *E*-allylamines **8A** and β-hydroxyamino compounds **7A**. Likewise, β-enehydrazino phosphonium salts **3'cH**, β-hydrazono phosphine oxides **3aH** and phosphonates **3bH** were obtained from hydrazines **1H** and phosphorylated allenes **2**. These derivatives were used for the two-carbon elongation of hydrazones and for the synthesis of azadienes **6H** and pyrazoles **9**, **10**.

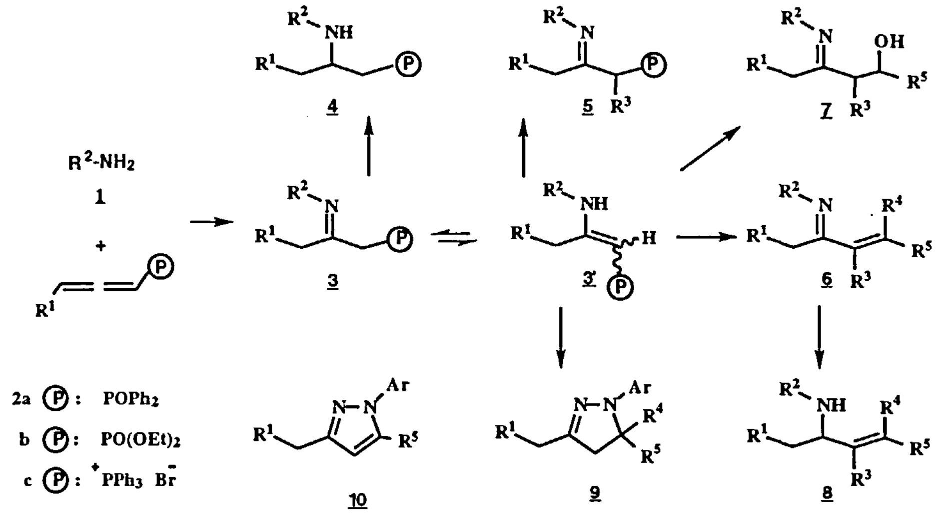
Imines[1] and hydrazones[2] are common nitrogen derivatives of ketones and aldehydes and have attracted a great deal of attention in recent years because of their range of applications.[1] They can be used not only as intermediates in heterocyclic synthesis,[3] but also in the enantioselective synthesis of natural products[4] and pharmaceuticals[5] of high enantiomeric purity. Particularly significant is the usefulness of α,β-unsaturated imines and hydrazones **1** as a result of their potential for the preparation of acyclic compounds,[6] as well as of the Diels-Alder reactivity of these substances as 1-azadienes for the construction of six membered heterocycles.[7] The lack of general methods for synthesis of these compounds has probably limited their use in organic synthesis. Simple α,β-unsaturated imines and hydrazones **6** are mostly synthesized by the condensation reaction of carbonyl compounds with hydrazines. However, the preparation of such compounds is far from simple and, specially in the case of ketones, only yields good results in very specific cases and generally leads to Michael addition.[8]

In recent years, we have used β-functionalized phosphorus derivatives as starting materials in the preparation of acyclic[9] and cyclic[10] derivatives. Continuing our interest in the reactivity of phosphorus substituted enamines and in the synthesis of azadienes[11] and in the preparation of homologation reagents of carbonyl derivatives into α,β-unsaturated imines[12] and hydrazones[13] with the introduction of two additional carbon atoms in the resulting chain, here we aim to extend this methodology to the preparation of a wide range of unsaturated compounds and to explore the synthetic use of β-functionalized phosphorus compounds in the preparation of new groups of acyclic and cyclic derivatives.

Synthesis of imino 5-7 and amino derivatives 4, 8A.

The preparation of the phosphine oxide derivative 3aA was very easily accomplished and in very high yields by means of simple addition of aliphatic, aromatic and functionalized amines 1A to phosphorylated allenes 2a in refluxing acetonitrile (see Scheme 1). Similarly, allenes derived from phosphonates 2b and phosphonium salts 2c also reacted with amines 1A to give the corresponding enamines 3'bA and 3'cA. Functionalized phosphine oxides 3aA and phosphonates 3'bA were used in the preparation of β-amino compounds derived from phosphine oxides 4aA and phosphonates 4bA by selective reduction of the carbon-nitrogen double bond, without affecting either the phosphine oxide, or the phosphonate and/or other functional groups present in compounds 3, when these derivative 3 were treated with $NaBH_4$ in refluxing ethanol.

Carbanions derived from imines such as metalloenamines are specially useful in organic synthesis.[1] In metalloenamines derived from compounds 3/3'A, the presence of an anion stabilising group such as phosphine oxide or phosphonate could control the deprotonation in the internal less substituted carbon. Thus, when compounds 3/3'aA and 3/3'bA were treated with methyl lithium followed by addition of alkyl halides and aqueous work-up, substituted compounds 5aA and 5bA were obtained (see Scheme 1). Similarly, the olefination reaction of derivatives 3/3'A were performed by treatment of these compounds 3/3'A with methyl lithium in THF and the resulting metalloenamine was then allowed to react with aliphatic, aromatic and heteroaromatic aldehydes to give 1-azadienes 6A. Michael addition of water to α,β-unsaturated imines 6A led to the formation of β-hydroxi-imino derivatives 7A. The treatment of azadienes 6A with an excess of $NaBH_4$ in ethanol-THF gave allylamines 8A. This procedure is highly stereoselective affording exclusively the *E*-stereoisomer.



A : $R^2 = R$; H : $R^2 = R_2N$

SCHEME 1

Synthesis of α,β-unsaturated hydrazones 6H and pyrazole derivatives 9 and 10.

β-Hydrazono 3a-cH and β-enehydrazino phosphorus compounds 3'a-cH could be suitable to efficiently achieve the homologation, or two carbon elongation, of hydrazones into their vinylogous compounds 6H. Thus, simple addition of hydrazines to allenes derived from phosphine oxides 2a and phosponates 2b led to the formation of hydrazones 3a,bH, while the use of allenes derived from phosphonium salts 2c afforded the β-enehydrazino phosphonium salts 3'cH isolated as a mixture of the *Z* and *E*-isomers (see Scheme 1).

Carbanions derived from hydrazones are useful intermediates in organic synthesis[2] and in our case are also used for the preparation of acyclic 6H, and cyclic compounds 9,10. Thus, phosphonium salts 3'cH were treated with a base (potassium carbonate) followed by Wittig reaction of the "in situ" generated phosphorane with aldehydes leading to α,β-unsaturated hydrazones 6H with high *E* stereoselectivity of the carbon-carbon double bond.The reaction with ketones failed. We extended this methodology for two carbon homologation of hydrazones, by using the corresponding β-functionalized phosphine oxides 3aH and phosphonates 3bH instead of phosphonium salts 3cH. In these cases, the metallation of β-hydrazono derivatives 3aH and 3bH with methyl lithium or LDA followed by the addition of ketones led to the formation of 1-azadienes 6H. This strategy can also be applied for five membered heterocycle formation when N-aryl hydrazones are used. Acyclic α,β-unsaturated compounds 6H (R_2N = ArNH) are formed by treatment of the starting hydrazones **3aH** (R_2N = ArNH) with two equivalents of a strong base like LDA followed by addition of aldehydes. Heating these compounds at 100°C caused intramolecular Michael addition and gave pirazoles **10**. However, when ketones reacted with dianion from phosphorylated hydrazones **3aH** (R_2N = ArNH) the pyrazolines **9** were obtained.

Acknowledgements. The present work has been supported by Dirección General de Investigación Científica y Técnica (DGICYT, PB 93-0 501) and by the Gobierno Vasco (GV, PI 9436). J.M. de los Santos (G. V.), J. García and E. Rodríguez (DGICYT) give thanks for their predoctoral fellowships.

REFERENCES

1. For reviews see: F. Wagner-Jauregg, Synthesis, 349 (1976). J. K. Whitesell and M. A. Whitesell, Synthesis, 517 (1983). For a recent review see: S. F. Martin in Comprehensive Organic Synthesis, Ed. B. M. Trost and I. Fleming; Pergamon Press: Oxford 2, 475 (1991).
2. For reviews see: Buckingham, Chem. Soc. Rev., 23, 37 (1969). Y. P, Kitaev and B. J Buzykin, Rus. Chem. Rev., 41, 495 (1972). For a recent review see: D. E. Bergbreiter and M. Momongan in Comprehensive Organic Synthesis, Ed. B. M. Trost and I. Fleming; Pergamon Press: Oxford. 2, 503 (1991).
3. J. Barluenga, V. Gotor, and F. Palacios, Synthesis, 642 (1975). L. Zhang, W. E. Meier, E J. Watson, and F. P. Gibson, Tetrahedron Lett., 35, 3675 (1994).
4. D. Enders and H. Baus, Ann. Chem., 1439 (1983). D. Enders, J. Tiebes, N. DeKimpe, M. Keppens, C. Stevens, G. Smagghe, and O. Betz, J. Org. Chem., 58, 4881 (1993). J. d'Angelo and D. Desmaele, Tetrahedron Lett., 31, 879 (1990).
5. T. N. Hart, D. Guillochin, G. Perrier, B. W. Sharp, H. P. Toft, B. Vacher, and R. J. A. Walsh, Tetrahedron Lett., 33, 7211 (1992). K. C. Nicolau, D. P. Papahatjis, D. A. Claremon, and R. E. Dolle III, J. Am. Chem. Soc., 103, 6967 (1981). G. Revial, Tetrahedron Lett., 30, 4121 (1989).
6. A. Hosomi, A. Shirahata, and H. Sakurai, Tetrahedron Lett., 19, 3043 (1978). A. Feuerer and T. Severin, Tetrahedron Lett., 34, 2103 (1993). E. Vedejs and D. M. Gapinski, Tetrahedron Lett., 22, 4913 (1981).
7. For a review see: D. L. Boger, in Comprehensive Organic Synthesis, Ed. B. M. Trost and I. Fleming; Pergamon Press: Oxford. 5, 451 (1991).
8. M. S. Gibson, The Chemistry of Amino Group, Ed. S. Patai and J. Willey. London: 61 (1968).
9. J. Barluenga, F. López, F. Palacios, F. H. Cano, and M. C. Foces-Foces, J. Chem. Soc. Perkin Trans I, 2329 (1988). J. Barluenga, I. Merino and F. Palacios, Tetrahedron Lett., 30, 1493 (1989).
10. J. Barluenga, F. López, and F. Palacios, Tetrahedron Lett., 28, 2875 (1987). F. López, E. Pelaez, F. Palacios, J. Barluenga, S. García, B. Tejerina, and A. García, J. Org. Chem., 59, 1984 (1994).
11. F. Palacios, G. Rubiales, and I. Pérez de Heredia, J. Org. Chem., 60, 2384 (1995). F. Palacios, C. Alonso, and G. Rubiales, Tetrahedron, 51, 3683 (1995).
12. F. Palacios, D. Aparicio, and J. García, Synlett, 261 (1994).
13. F. Palacios, D. Aparicio, and J. M. de los Santos, Tetrahedron Lett., 34, 3481 (1993).