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A Simple and Efficient Synthesis of α,β-Unsaturated Hydrazones from Functionalized Ylides and Phosphine Oxides

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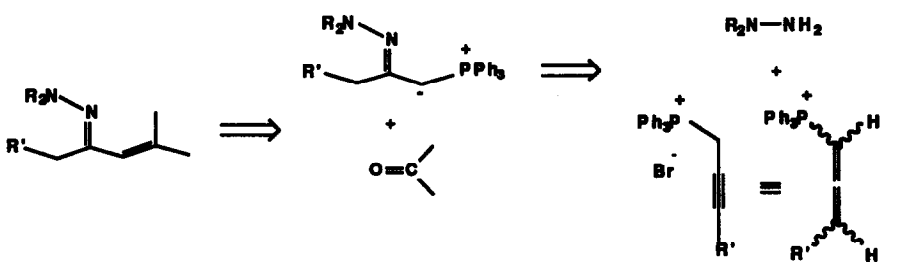
Key Words: Hydrazones, 1-Azadienes, Phosphorus ylides, Phosphine oxides.

Abstract: A simple and very efficient route to α,β-unsaturated hydrazones derived from ketones has been developed. These compounds are obtained through Wittig reaction of the phosphoranes generated "in situ" from β-enhydrazino phosphonium salts with aldehydes and olefination reaction of phosphine oxides derived from hydrazines.

Hydrazones have attracted a great deal of attention because they are very important building blocks in organic synthesis[1]. They have been extensively used not only as intermediates in heterocyclic synthesis[2], but also in the asymmetric synthesis of chiral amines[3], pharmaceuticals and food additives of high enantiomeric purity[4]. Particularly significant is the utility of α, β-unsaturated hydrazones as a result of their potential as starting materials in the preparation of β-hydroxi[5], α, β-unsaturated ketones[6], biologically active pyrazols[7], as well as the Diels-Alder reactivity of these substances as 1-azadienes for the construction of six membered heterocycles[8].

Simple α, β-unsaturated hydrazones are mostly synthesized by condensation reaction of carbonyl compounds with hydrazines[9]. 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[9]. In this context, it is noteworthy that an elegant approach to the preparation of α, β-unsaturated hydrazones has been recently reported, making use of phosphonium salts[10], although this method is limited to the preparation of hydrazones derived from aldehydes.

In the last years, we have used phosphorylated enamines as starting materials in the preparation of acyclic[11] and cyclic[12] derivatives. Continuing our interest in the reactivity of phosphorus substituted enamines and in the synthesis of azadienes[13], we wish to report herein our initial findings on the use of easily available β-enhydrazino phosphonium salts and β-hydrazino phosphine oxides as reagents for the synthesis of 1-azadienes from commercially available starting reagents, such as propargyltriphenylphosphonium bromide, hydrazines and aldehydes through olefination reaction of the corresponding functionalized phosphoranes. (Retrosynthetic pathway, see scheme).



Scheme

The desired β-enhydrazino phosphonium salts **2** required to obtain the phosphorane **3** are very easily prepared in very high yields through nucleophilic addition of achiral and chiral hydrazines to propargyltriphenylphosphonium bromide **1** in refluxing of chloroform. The structure of **2** was ascertained on the basis of their spectroscopic data[14], which indicate that they are isolated as a mixture of the *Z*- and *E*-substituted phosphonium salts **2**, although separation of *Z*- and *E*- isomers is not necessary for subsequent reactions. Conversion to the phosphorane **3** using a base and by reaction with aliphatic, heteroaromatic and aromatic aldehydes (see table 1) leads to the corresponding 1-azadienes **4**. Pure compounds were obtained after flash-chromatography and show satisfactory microanalyses. Reactions with ketones failed. *n*-Butyl lithium was the initial base chosen for the "in situ" generation of **3**. Owing to the partially stabilised nature of this phosphorane it was thought that a weaker base would suffice, although the phosphorane could not be isolated. Thus, the preferred choice was potassium carbonate in DMF, which requires no special precautions and provides excellent yields. Spectral data are in agreement with structure **4**[15], in which vicinal coupling constants of 16.5 Hz for the vinylic position of **4b** evidenced *E* configuration of the carbon-carbon double bond.

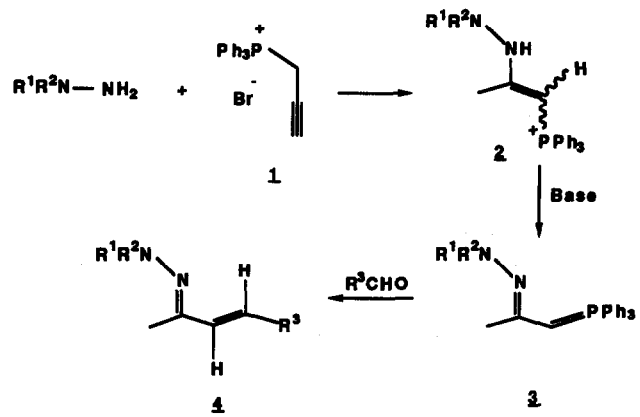
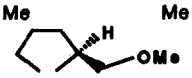
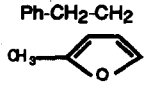
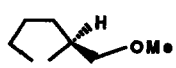


Table 1. Compounds **2** and **4** obtaniend.

	R^1	R^2	R^3	yield(%)	m.p.(°C)
2a	Me	Me		88[a]	216-217
2b				85[a]	159-160
4a	Me	Me	Ph	82[b]	oil[c]
4b	Me	Me	Me-Ph	81[b]	oil[c]
4c	Me	Me	Ph-CH_2-CH_2	91[b]	oil[c]
4d	Me	Me		81[b]	oil[c]
4e			Me-Ph	88[b]	oil[c]

[a] Yield of isolated products **2** based on **1**; [b] Yield of isolated products **4** based on **2**;

[c] Purified by flash chromatography.

To increase the usefulness of this methodology in synthesis, reaction with ketones was required. Hence the functionalised phosphine oxides **6** are prepared through a similar strategy to the above described using phosphine oxides allenes **5**. Thus, reaction of hydrazines with substituted allenes **5** leads to the formation of phosphorus derivatives **6**[16] in very high yields. Metalation of **6** was performed by using methyl lithium or lithium diisopropylamide (LDA) in THF at -78ºC. The resulting lithium salt was then allowed to react with aldehydes and ketones (25ºC, 1d, THF) and after aqueous work-up and flash-chromatography compounds **4** gave excellent yields (table 2). In the case of aldehydes, reaction products were identical with those obtained by reaction of phosphoranes with aldehydes.

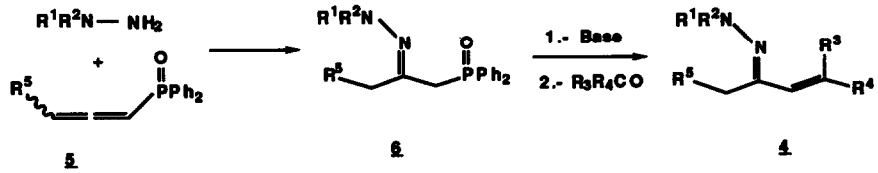
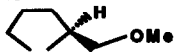
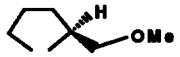


Table 2. Compounds **6** and **4** obtained.

	R^1	R^2	R^3	R^4	R^5	yield(%)	m.p.(ºC)
6a	Me	Me			H	89[a]	107-108
6b					H	90[a]	91-92
6c	Me	Me			Me	86[a]	98-99
4f	Me	Me	Ph	Ph	H	80[b]	oil[c]
4g	Me	Me		$(CH_2)_5$	H	86[b]	oil[c]
4h	Me	Me	H	Me-Ph	Me	85[b]	oil[c]
4i			H	Ph	H	93[b]	oil[c]

[a] Yield of isolated products **6** based on **5**; [b] Yield of isolated products **4** based on **6**; [c] Purified by flash chromatography.

In summary, we describe a remarkably simple, high yielding route to α, β-unsaturated hydrazones (1-azadienes) derived from ketones using readily available starting materials and under mild reaction conditions, making this process a complement to the previously reported method[10]. These systems could be key intermediates in the synthesis of acyclic[1-6] and cyclic[7,8] compounds. Further studies about compounds **4** are in progress and will be reported in due course.

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REFERENCES AND NOTES

1.- Rozen, S; Zamir, D. *J. Org. Chem.*, **1991**,*56*, **4695**. For a review see; Bergbreiter, D.E.; Momonjau, M. in "Comprehensive Organic Synthesis" Ed. B.M. Trost and I. Fleming, Pergamon Press, Oxford **1991**, *Vol. 2*, p. 503.

2.- Barluenga, J.; Gotor, V.; Palacios, F. *Synthesis* **1975**, 642; Baccolini, G.; Sgarabotto, P. *Chem. Commun*, **1991**, *34*.

3.- Burk, M.J.; Feaster, J.E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

4.- For a review see; Enders, D. in *"Asymmetric Synthesis"*, Ed. J.D. Morrison, Academic Press, New York, **1984**, *Vol. 3*, p. 275.

5.- Hagashi, T.; Matsumoto, Y.; Kiyoi, T.; Ito, Y.; Kohra, S.; Tominaga, Y.; Hosomi, A. *Tetrahedron Lett.*, **1988**, *29*, 5667.

6.- Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.*, **1978**, 3043.

7.- Patel, H.V.; Vyas, K.A.; Pandey, S.P.; Tavares, F.; Fernandes, P.S. *Synlett*, **1991**, 483.

8.- For a review see; Boger, D.L.; Weinreb, S.M. in *"Hetero Diels-Alder Methodology in Organic Synthesis"*, Academic Press, San Diego, **1987**, p. 239; Serckx-Poncin, B.; Hesbain-Frisque, A.M.; Gosez, L. *Tetrahedron Lett.*, **1982**, *23*, 3261; Waldner, A. *Tetrahedron Lett.*, **1989**, *30*, 3061; Nebois, P.; Fillion, H.;*Tetrahedron Lett.*, **1991**, *32*, 1307; Allcock, S.J.; Gilchriat, T.L.; King, F.D. *Tetrahedron Lett.*, **1991**, *32*, 125.

9.- Gibson, M.S. in *"The Chemistry of Amino Group"*, Ed. S. Patai, J. Willey, London, **1968**, p. 61.

10.- Cristau, H.J.; Gasc, M.B. *Tetrahedron Lett.*, **1990**, *31*, 341.

11.- Barluenga, J.; López, F.; Palacios, F.; Cano, F.H.; Foces-Foces, M.C. *J. Chem. Soc. Perkin Trans I*, **1988**, 2329; Barluenga, J.; Merino, I.; Palacios, F. *Tetrahedron Lett.*, **1989**, *30*, 1493.

12.- Barluenga, J.; López, F.; Palacios, F. *Tetrahedron Lett.*, **1987**, *28*, 2875; Barluenga, J.; López, F.; Palacios, F. *J. Chem. Soc. Perkin Trans I*, **1989**, 2273.

13.- Barluenga, J.; Ferrero, M.; Palacios, F. *Tetrahedron Lett.*, **1988**, *29*, 4863.

14.- Spectral data of **2a**: ^{1}H-RMN ($CDCl_3$, TMS, 300 MHz) δ *Z*-isomer: 1.74(s, 3H, CH_3); 2.71(s, 6H, CH_3-N); 4.60(d, 1H, $^{2}J_{PH}$=18Hz, CH); *E*-isomer: 2.06(s, 3H, CH_3); 2,32(s, 6H, CH_3-N); 3.58(d, 1H, $^{2}J_{PH}$=19Hz, CH); 7.26-7.75(m, 15H, Arom); 9.72-10.00(s, NH) ppm; ^{13}C-RMN ($CDCl_3$, TMS, 75MHz) δ *Z*-isomer: 21.9(CH_3); 45.8(N-CH_3); 54.5(d, $^{1}J_{PC}$=117Hz, CH); 164.2(C=N); *E*-isomer: 22.1(CH_3); 46.0(CH_3-N); 53.5(d,$^{1}J_{PC}$=123Hz, CH); 164.4(C=N); 122.8-133.8(C-Arom) ppm; ^{31}P-RMN ($CDCl_3$, PO_4H_3, 120MHz)δ 11.8(*E*-isomer); 17.4(*Z*-isomer) ppm; MS *m/e* 360(M^{+}-HBr).

15.- Spectral data of **4b**: ^{1}H-RMN ($CDCl_3$, TMS, 300MHz)δ 2.17(s, 3H CH_3); 2.33(s,3H, CH_3) ;2.53(s, 6H, CH_3-N); 6.89(d, 1H, $^{3}J_{HH}$=16.5Hz, =CH); 7.11-7.58(m, 5H, Arom + CH=) ppm; ^{13}C-RMN ($CDCl_3$, TMS, 75MHz)δ 13.4(anti CH_3); 20.4(syn CH_3); 21.3(CH_3-Arom); 47.3(anti CH_3-N); 48.1(syn CH_3-N); 119.4-139.1(C-Arom); 161.4(syn C=N); 162.7(anti C=N)ppm;

16.- Spectral data of **6a**:^{1}H-RMN ($CDCl_3$, TMS, 300MHz)δ 2.08(s, 3H, CH_3); 2.18 and 2.22(s, 6H, anti and syn CH_3-N); 3.33(d, 2H, $^{2}J_{PH}$=14.3Hz, syn CH_2); 3.73(d, 2H, $^{2}J_{PH}$=14.9Hz, anti CH_2); 7.27-7.77(m, 10H, C-Arom) ppm; ^{13}C-RMN ($CDCl_3$, TMS, 75MHz)δ 18.6(syn CH_3); 24.2(anti CH_3); 33.7(d, $^{1}J_{PC}$=64Hz, anti CH_2); 41.3(d, $^{1}J_{PC}$=64.5Hz, syn CH_2); 46.3(syn CH_3-N); 46.6(anti CH_3-N); 127.9-133.1(C-Arom); 159.9(syn C=N); 160.0(anti C=N) ppm; ^{31}P-RMN ($CDCl_3$, PO_4H_3, 120MHz)δ 29.5(syn); 27.8(anti) ppm.

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