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Condensation of Lithium Diphenylphosphonium Diylides with Carbonic Anhydride Derivatives. A New One-Pot Synthesis of α,β-Unsaturated Anilides and Amidines.

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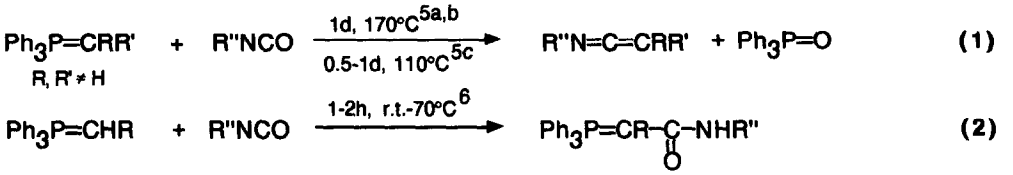
Key Words : lithium phosphonium diylides; pseudo-acylation reaction; Wittig reaction; vinylic amides and amidines.

Abstract : Lithium diphenylphosphonium diylides readily attack phenylisocyanate and dicyclohexylcarbodiimide. The formed semi-stabilised ylides bear a metallated amide or amidine function. Their use in situ as Wittig reagents towards aldehydes and ketones is shown to be a new one-pot, E-stereoselective synthesis for α,β-unsaturated anilides and amidines. Moreover, the corresponding phosphonium salts were isolated.

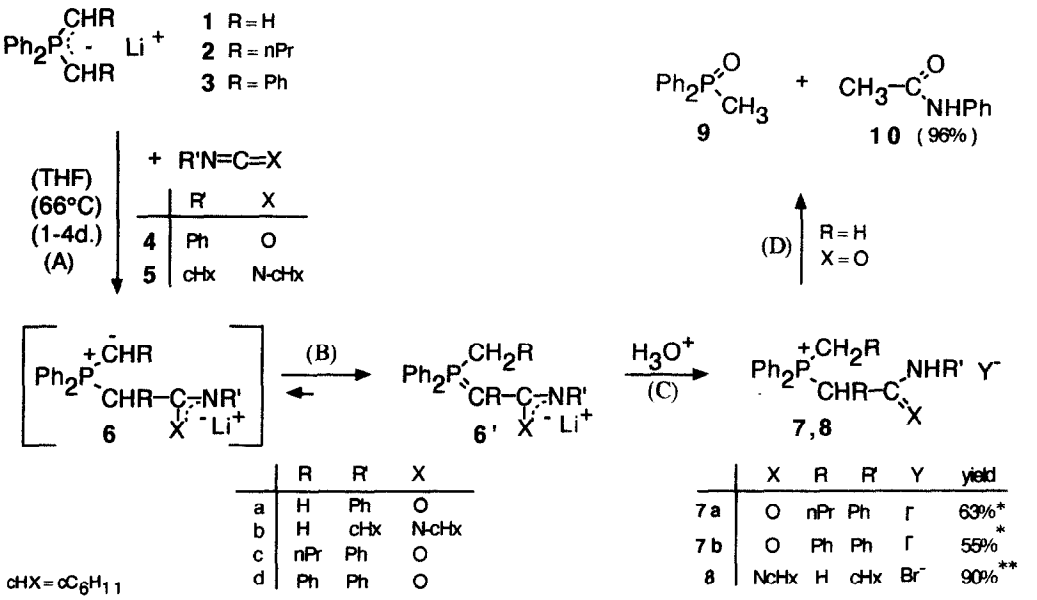
Apart from one attempt [1], the reactivity of lithium phosphonium diylides with regard to organic substrates had never been studied until we published our first results in 1987-88 [2]. Following this, research started on the study of stereochemistry of the Wittig reaction of diylides with aldehydes and ketones [3]. Our work showed the potential synthetic interest of diylides in contrast to classical monoylides, due essentially to a greater nucleophilicity, in different reactions with such carbon substrates as esters, amides or carbonic acid derivatives [2,4].

Now, our attention is turned to a new series of electrophilic substrates. Two CO_2 derivatives, whose reactive centres are sp-carbon atoms (an isocyanate and a carbodiimide) were investigated in order to compare our results to the known behavior of monoylides. Disubstituted monoylides react with isocyanates to yield ketenimines by a Wittig-type reaction [5] (see equation 1). Non-substituted or mono-substituted monoylides are known to condense with isocyanates to produce stabilised ylides [6] (see equation 2).



As far as carbodiimides are concerned, even if the reaction of monoylides with diphenylcarbodiimide is known, similar to equation 2, the same authors detect no reaction with DCC, due to a lack of activation [7].

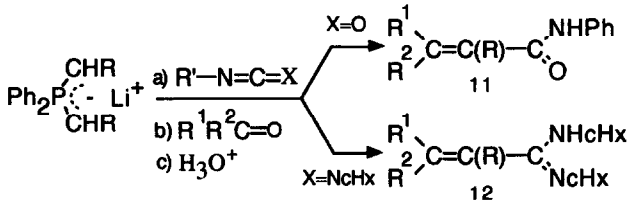
Herein, we report that the differently substituted diylides **1, 2, 3** react with phenylisocyanate **4** and DCC **5**, in a pseudo-acylation way (Scheme 1). The complete attack of diylide **1** upon isocyanate **4** occurs easily (step A). The intermediary adduct **6** is transformed into a pseudo-acylated monoylide **6'** thanks to an intramolecular transylidation (step B). After acidic hydrolysis (step C), the phosphonium salt was transformed quantitatively into phosphine oxide **9** and acetanilide **10** (step D). Those two products could result from a Wittig-type reaction (**10** being the hydrolysis product of N-phenylketenimine). However, both results obtained with mono-substituted diylides **2** and **3** towards isocyanate **4** confirmed the exact route to be an adduct-formation. The adducts **6'** were unambiguously characterised by isolation of the corresponding phosphonium salts **7a, b** and by ^{31}P NMR in the case of diylide **1** [adduct **6'a** : δ = 8,7 ppm (s)]. For DCC **5**, a similar reaction pathway is observed, as the phosphonium salt **8** was obtained after acidic work-up.



Scheme 1 : (*) isolated yields; (**) ^{31}P-NMR formation ratio.

For both initial substrates **4** and **5**, the intermediate adducts **6'** are interesting monoylides prepared *in situ*, bearing a metallated α-function. Thus, they can be used as Wittig reagents without any purification, in a one-pot procedure. The efficiency of such a synthetic route to α,β-unsaturated anilides and amidines has been probed as shown below : Scheme 2. For **6'a** and **6'b**, both cinnamanilide and cinnamamidine are obtained in good yield and E-stereoselectivity from benzaldehyde. In the case of monoylide **6'a** (from **1** and **4**), we checked a generalisation of the method applying to other carbonyl compounds. With trans-cinnamaldehyde, the results are similar. Moreover, thanks to its enhanced nucleophilicity due to metallation of the stabilising group, the adduct **6'a** can even react with such unreactive ketones as benzophenone. The E-stereoselectivity remains good with acetophenone. The last two yields could not be increased by refluxing THF. In the case of benzophenone, the

remaining ketone can be isolated, whereas with acetophenone the yield of recovered ketone is low. In that case, deprotonation at the α position may have occured, so that the amido group of **6'** is no longer metallated, and the corresponding stabilised ylide becomes unreactive towards ketones. After acidic work-up, ketolization products together with acetanilide **10** have been isolated.



	X	R	R^1	R^2	isolated yield	Z/E[α]
11a	O	H	Ph	H	77	0/100
11b	O	H	styryl	H	75[β]	0/100
11c	O	H	Ph	Me	40	16/84[δ]
11d	O	H	Ph	Ph	51	——
11e	O	nPr	Ph	H	42	22/78[ε]
11f	O	Ph	Ph	H	37	18/82[ε,η]
12	NcHx	H	Ph	H	80[γ]	0/100

Scheme 2 : α) ^{1}H-NMR (250 MHz). β) formation ratio. γ) pure amide from basic hydrolysis of **12**. δ) product before chromatography; pure isolated : Z/E = 13/87. ε) non attributed stereochemistry. (η) GC/MS.

In conclusion, we have developed the reactions of diylides with isocyanates and carbodiimides, and have shown their synthetic application for the one-pot preparation of β-substituted N-substituted amides and amidines.

Typical procedure for the *in situ* preparation of 6' [9] : To diylide [8] **1-3** (5.0 mmoles) in THF (100 ml) was added dropwise **4** (5.0 mmoles, freshly distilled) or **5** (6.0 mmoles), in THF (25 ml). The mixture was refluxed in THF for 1 day (diylide **1**) or 4 days (diylides **2, 3**).

Preparation of 7 : Monoylide **6'c** or **6'd** prepared as above was hydrolysed at 0°C with 25 ml HCl (0.5 N). After solvent evaporation under reduced pressure, extraction with $CHCl_3$, drying over Na_2SO_4 and concentration, the residue was separated by column chromatography on silica gel. The phosphorus compound eluted was washed with 10 ml HCl (0.5 N), submitted to anion-exchange with NaI/H_2O, and afforded after recrystallization ($CHCl_3$/EtOAc) : **7a** [11] : 1.72 g (3.15 mmoles, 63%, mp 174.1°C); **7b** [12] : 1.55 g (2.70 mmoles, 55%, mp 210°C).

Preparation of 8 : Monoylide **6'b** prepared as above was hydrolysed at room temperature with HCl (0.5 N) in excess. After solvent evaporation under reduced pressure, extraction with CH_2Cl_2, drying of the extracts over Na_2SO_4 and concentration, a precipitation of the residue dissolved in a minimum $CHCl_3$, in 0.5 l dry Et_2O afforded the salt **9** : ^{31}P-NMR (CH_2Cl_2) δ 21.8 ppm (90% formation rate).

Typical Wittig reaction procedure of 6' with aldehydes and ketones [9] **:** To monoylide **6'** (5.0 mmoles) in THF (100 ml) was added dropwise aldehyde or ketone (10.0 mmoles) in THF (25 ml). The mixture was stirred at room temperature for 1 day (**6'a** + PhCHO), 2 days (**6'b** or **6'c** + PhCHO), 4 days (**6'a** + PhCH=CH-CHO), or 5 days (**6'a** + ketone) or refluxed for 2 days (**6'd** + PhCHO), and hydrolysed with HCl (0.5 N). After solvent evaporation under reduced pressure, extraction with CH_2Cl_2, drying of the extracts over Na_2SO_4 and concentration, a separation by chromatography on silica gel (CH_2Cl_2/Hexane 5/5 to 10/0 ; CH_2Cl_2 + 1-3% MeOH) afforded the pure anilides **11a-f** in the corresponding yields (scheme 2), and the crude amidine **12**. All anilides **11** were characterized by mp (in agreement with the literature), IR (KBr), ^{1}H NMR (250 MHz) and GC/MS (pos E.I). After identification by GC/MS (pos. E.I. : M^+=310), crude **12** was

dissolved in diglyme (60 ml), added to NaOH 20% (20 ml) and refluxed for 3 days. After acidification (pH = 5-6) with HCl (0.5 N) and similar work-up as above, a separation by chromatography on silica gel (CH_2Cl_2/Hexane 7/3) afforded the corresponding amide (0.92 g ; 4.0 mmoles ; 80% yield), characterized by mp (in agreement with the literature), IR (KBr), ^{1}H-NMR (250 MHz) and GC/MS (pos. E.I.).

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8. Typical procedure for the preparation of diylides **1-3**[9] : nBuLi (10.0 mmoles ; 1.6N ; titrated before use according to Gilman's method[10] in hexane or Et_2O, was added dropwise below -50°C to the phosphonium salt (5.0 mmoles ; 1.71g $Ph_2Me_2P^+ I^-$; 2.13 g $Ph_2nBu_2P^+ Br^-$: 2.24 g $Ph_2(PhCH_2)_2P^+ Br^-$) suspended in THF (100 ml). The mixture was stirred for 10 min at -50°C and warmed to room temperature for about 1h. ^{31}P NMR : **1** : 30.9 ppm ; **3** : 12.0 ppm.
9. All manipulations were performed with dry THF under a dry oxygen-free nitrogen atmosphere.
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11. **7a** : IR (KBr) 1688 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 0.9 (t dist., 6H), 1.1-2.0 (m, 8H), 2.5-3.3 (m, 2H), 5.8 (m, 1H), 7.0-8.4 (m, 15H), 10.8 (s broad,1H) ; ^{31}P-NMR ($CHCl_3$) δ 29.6 (s) ; Anal. Calcd. for $C_{27}H_{33}NOPI$: C 59.45 ; H 6.10 ; N 2.57 ; P 5.68 ; I 23.26. Found : C 58.50 ; H 6.10 ; N 2.33 ; P 5.35 ; I 22.56).
12. **7b** : IR (KBr) 1670 cm^{-1} ; ^{1}H-NMR ($CDCl_3$) δ 4.43 (d, J=14.0Hz, 2H), 6.6 - 8.1 (ma 26H), 11.31 (s broad, 1H) ; ^{31}P-NMR ($CHCl_3$) δ 28.92 (s) ; Anal. Calcd for $C_{33}H_{29}NOPBr$: C 69.97 ; H 5.28 ; N 2.47 ; P 5.47. Found : C 70.17 ; H 5.22 ; N 2.40 ; P 5.25.

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