SOLID-PHASE ORGANIC SYNTHESIS: CREATION OF CARBON–CARBON DOUBLE BONDS UNDER MILD CONDITIONS BY WITTIG-TYPE REACTIONS*

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Phosphorane ylides and phosphonate anions react smoothly with resin-bound aldehydes and ketones to provide alkenes in good yields and purities (assessed after cleavage of acid-labile PAL anchor to support). The reactions of aldehydes give excellent stereoselectivities. Effective conditions have been developed for carrying out these transformations.

Key words: Solid-phase synthesis; Combinatorial chemistry; Wittig reaction.

Solid-phase combinatorial chemistry, combined with sensitive methods for on- or off-bead biological screening, has attracted much recent attention as an approach for drug lead discovery and optimization[2–11]. Although initial efforts in this library area were focused on short peptides assembled by repetitive cycles of solid-phase synthesis chemistry, the current goals of the field are to develop a repertoire of methods to access essentially any small organic structure in the 100 to 1 000 molecular weight range. The present communication describes how the widely useful Wittig reaction[12], including the Horner–Wadsworth–Emmons modification[13], can be adapted to the solid-phase mode.****

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**** The application of resin-bound phosphines to Wittig chemistry was described in refs[14,15], and of a Homer–Wadsworth–Emmons variation in ref.[16]. In these literature approaches, the usually difficult-to-remove triphenylphosphine oxide now becomes retained on the support while the product alkene is released into solution. The approaches of the present paper are reciprocal to the ones described in refs[14–16] in that they leave the desired product alkene on the support for further transformations. Other examples are reported in refs[17,18].

The solid-phase organic synthetic work described herein was carried out on polyoxyethylene–polystyrene (POE–PS)* graft supports, which were introduced and pioneered for peptide synthesis and other applications by Bayer and Rapp[19]. Since these beaded polymers have become available commercially, known as TentaGelS, they have been used widely in the field due to their good mechanical stability, compatibility with a range of organic reagents and solvents, and sufficient hydrophilic character to allow for later biological testing carried out in aqueous milieus. Pendant amino groups of POE–PS were the point of attachment for the acidolysable tris(alkoxy)benzylamide (PAL) handle[20], and *N*-Fmoc-*p*-nitrophenylalanine was added by standard DIPCDI/HOBt-mediated coupling. Fmoc removal to release free amino functions was achieved by treatment with piperidine–DMF (1 : 4) at 25 °C for 2 + 10 min. This experimental design ensured that following solid-phase organic synthesis and cleavage of the PAL linkage, all products would have a terminal Nph-NH_2 residue which would serve as a chromophoric group for convenient HPLC detection (Fig. 1).

The title reactions required resin-bound carbonyl functions. Three ways were explored to achieve this: (i) introduction of hydroxyl group-containing building blocks, and subsequent oxidation[21,22],**, (ii) introduction of acetal-protected building blocks, and subsequent hydrolysis with mild acid[23,24]; and (iii) direct coupling of ω-carboxy

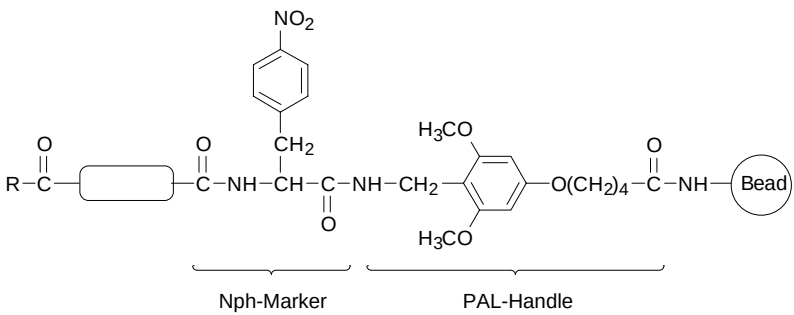


FIG. 1
General structure of substrates for solid-phase Wittig-type reactions

* The following abbreviations are used: DBU, 1,8-diazobicyclo[5,4,0]undec-7-ene; DIEA, *N,N*-diisopropylethylamine; DIPCDI, *N,N*'-diisopropylcarbodiimide; DMF, *N,N*-dimethylformamide; Fmoc, 9-fluorenylmethyloxycarbonyl; HOBt, 1-hydroxybenzotriazole; KHMDS, potassium bis(trimethylsilyl)amide; Nph, *p*-nitrophenylalanine; PAL, 5-(4-(Fmoc)aminomethyl-3,5-dimethoxyphenoxy)valeric acid handle; POE–PS, polyoxyethylene–polystyrene graft support; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

** In our hands, oxidations of aliphatic primary alcohols gave either no reaction, or complex mixtures both on-resin and for solution controls. Better results were obtained on secondary alcohols.

TABLE I
Reactions of a variety of ylides with resin-bound carbonyl-containing substrates[a]

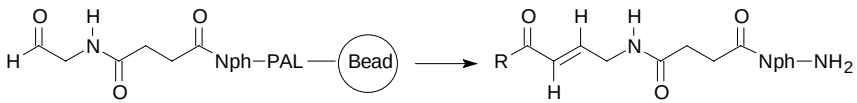
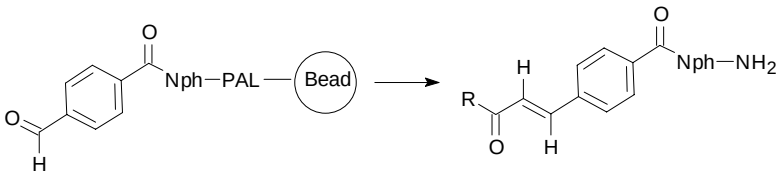
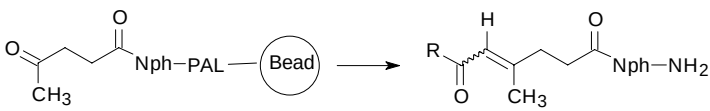
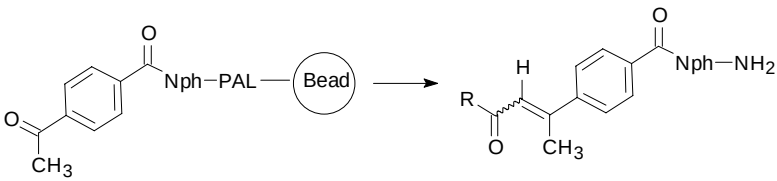
No.	Reagent	R	Solvent	Base	Temperature °C	Time h	Purity %
							
1	$Ph_3P{=}CHCO_2CH_3$	OCH_3	THF	–	65	2	75[b]
2	$Ph_3P{=}CH(C{=}O)CH_3$	CH_3	CH2Cl$_2$	–	45	2	70[b]
3	$(EtO)_2P(O)CH_2CO_2Et$	OEt	CH_3CN[c]	LiBr/DIEA	25	1	78[b]
							
4	$Ph_3P{=}CHCO_2CH_3$	OCH_3	THF	–	65	1	78[b]
5	$Ph_3P{=}CH(C{=}O)CH_3$	CH_3	CH_2Cl_2	–	45	2	90[b]
6	$(EtO)_2P(O)CH_2CO_2Et$	OEt	CH_3CN[c]	LiBr/DIEA	25	1	86[b]
7	$(CF_3CH_2O)_2P(O)CH_2CO_2CH_3$	OCH_3	CH_3CN[c]	LiBr/DIEA	25	1	91[d]
							
8	$(EtO)_2P(O)CH_2CO_2Et$	OEt	CH_3CN[e]	LiBr/DBU	50	10	70
9	$(EtO)_2P(O)CH_2CO_2Et$	OEt	THF[f]	KHMDS	25	1	75

TABLE I
(*Continued*)

No.	Reagent	R	Solvent	Base	Temperature °C	Time h	Purity %
							
10	$(EtO)_2P(O)CH_2CO_2Et$	OEt	CH_3CN[e]	LiBr/DBU	50	5	75
11	$(EtO)_2P(O)CH_2CO_2Et$	OEt	THF[f]	KHMDS	25	1	75

[a] General explanation is in Experimental, and specific additional details are in the footnotes which follow. [b] Stereoselectivity was $E : Z > 20 : 1$, as judged by chemical shift and coupling constants of vinylic protons. [c] The phosphonate (0.5 mmol) in dry CH_3CN solution was combined with dry LiBr (43 mg, 0.5 mmol) and DIEA (77 μl, 0.45 mmol), stirred for 5 min at 25 °C, and then added to the resin-bound aldehyde (500 mg, 0.1 mmol). [d] Stereoselectivity was $Z : E > 20 : 1$, as judged by chemical shift and coupling constants of vinylic protons. [e] The phosphonate (1.0 mmol) in dry CH_3CN solution was combined with dry LiBr (86 mg, 1.0 mmol; for these reactions, the salt was placed in the reactor vessel first and heated to remove last traces of water), DBU (142 μl, 0.95 mmol), and 12-crown-4 (16 μl, 0.1 mmol), stirred under argon for 5 min at 25 °C, and added to the resin-bound ketone (500 mg, 0.1 mmol). In separate experiments, we found that omission of crown ether (these are recommended in the literature) did not substantially affect the yield and purity of the product. [f] In a flame-dried 10-ml glass flask, the phosphonate (0.2 mmol) was combined with 18-crown-6 (26 mg, 0.1 mmol) in dry THF (1 ml), and 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (0.36 ml, 0.18 mmol) was added dropwise at –78 °C. Stirring continued for 1 h at 25 °C prior to addition of the anion-containing reaction mixture to the resin-bound substrate. The reaction was quenched by addition of AcOH–toluene (1 : 9), following which the resin-solvent slurry was transferred to a syringe reactor for further washings and cleavage as described in Experimental. Conclusion in note *e* about crown ether applies to these studies as well.

aldehydes and ketones. Subsequently, treatments with a variety of phosphorane ylides or phosphonate anions provided alkenes. Stabilized phosphoranes quantitatively transformed aliphatic and aromatic aldehydes (no starting materials remaining) and gave *E*-olefins in good yields, purities, and stereoselectivities, as verified by ^{1}H NMR and HPLC analyses of products released by acidolysis (Table I, lines 1, 2, 4, and 5). However, corresponding reactions when using ketone-containing substrates in place of aldehydes were sluggish or did not occur at all (>95% of starting material recovered).

The more reactive species derived from treatment of phosphonates with a tertiary amine in the presence of lithium bromide also smoothly transformed aldehydes to alkenes

(Table I, lines 3, 6, and 7). When triethyl phosphonoacetate was used, only *E*-alkenes were obtained, but the stereochemistry was reversed[25] when using bis(2,2,2-trifluoroethyl) (methoxycarbonyl)phosphonate. Polymer-supported ketones reacted poorly under standard conditions, but excellent conversions were achieved by addition of the strong base DBU *in the presence of dry lithium bromide*[26,27], or the potassium salt of hexamethyldisilazane (KHMDS). When such strong bases are applied, it is critical to use a stable linker such as PAL; substantial cleavage of *p*-alkoxybenzyl esters (e.g., Wang-resin) occurred under the reaction conditions. The solid-phase Horner–Wadsworth–Emmons reactions of ketones gave approximately 1 : 1 mixtures of *E* and *Z* stereoisomers.

EXPERIMENTAL

Four sets of solid-phase reactions are described in Table I. The resin-bound substrate for the first set was obtained by acylation of H-Nph-PAL-resin with succinic anhydride–DIEA (5 equivalents each) in CH_2Cl_2, 2 h, 25 °C, to reach a ninhydrin-negative support, then adding aminoacetaldehyde dimethyl acetal by a DIPCDI/HOBt-mediated coupling, and finally removing the dimethyl acetal protecting group with $LiBF_4$ (2 equivalents) in H_2O–CH_3CN (1 : 49), 1 h, 25 °C. The resin-bound substrates for the remaining sets were obtained by DIPCDI/HOBt-mediated couplings (quantitative) of *p*-carboxybenzaldehyde, levulinic acid, and *p*-acetylbenzoic acid, respectively, to the H-Nph-PAL-resin. Except for Table I, lines 9 and 11 (covered in footnote *f* to Table I), the carbonyl-containing resin-bound substrate (500 mg, 0.2 mmol/g, 0.1 mmol) drawn on the left side of each equation was placed in a 5-ml syringe fitted with a porous frit to facilitate filtration on the syringe bottom and a rubber septum over the top, and washed carefully with dry solvent. For and during reactions and washes, the apparatus was flushed and maintained under argon by means of a stainless steel needle immersed into the resin-solvent-reagent slurry; this gas flow also provided gentle agitation of the reactions. A solution of the appropriate ylide (0.2 mmol for Table I, lines 1, 2, 4, 5, 9, and 11; or larger amount as specified in footnotes *c* and *e* to Table I) derived from the reagent listed in the left column, dissolved in the indicated dry solvent (1 ml), was injected into the syringe reactor, and the reaction was allowed to proceed under the indicated conditions. Phosphorane ylides (Table I, lines 1, 2, 4, and 5) were commercially available; phosphonate anions were prepared in situ as described in footnotes *c*, *e* and *f* to Table I. Filtration and washing with THF, CH_2Cl_2, DMF, and CH_2Cl_2 (4 × 2 ml, each solvent) was followed by cleavage by 1 ml TFA–H_2O (19 : 1), 90 min, 25 °C. The filtrate from the cleavage was collected, concentrated in vacuo, and analyzed by RP-HPLC (C_{18} column developed with gradient of 0.1% aqueous TFA and CH_3CN), ^1H NMR spectroscopy, and electrospray MS or FAB-MS to establish the structures and purities (relative integrations in HPLC, monitored by absorbance at 220 nm) of the products drawn on the right side of the equation.

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