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Application of Polymer-Bound Phosphonium Salts as Traceless Supports for Solid Phase Synthesis

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Abstract: The utility of the phosphonium group as a traceless linker for the solid phase synthesis of small organic molecules is demonstrated by the elaboration of polymer-bound phosphonium salts and their subsequent cleavage to alkyl, alkenyl and heteroaryl products.
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In recent years, concepts developed for the solid phase synthesis of peptides and oligonuleotides have been shown to be equally applicable to the synthesis of small, non-oligomeric organic molecules.[1,2] The ability to prepare such compounds by solid phase methods has been a major driving force behind the important and rapidly growing field of combinatorial chemistry.[3]

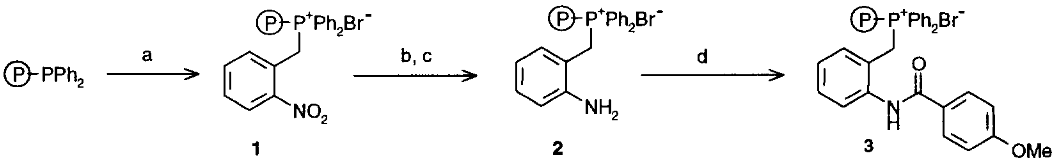
As a result of more than three decades of activity in solid phase oligomer synthesis, a large number of linker groups have been developed to immobilise compounds *via* polar groups such as carboxylic acids, amides and alcohols. With the growing interest in solid phase synthesis of a more diverse range of smaller molecules, a need has arisen for an expanded range of linker groups. Of particular value are so-called "traceless" linkers which leave no memory in the cleaved product of the group used to tether the molecule to its support. To this category belong aryl silane linkers[4,5] which are cleaved by protodesilylation to unsubstituted aromatics and a photolabile benzyl sulfide[6] used to prepare methyl biphenyls. Recently the Horner-Wadsworth-Emmons reaction has been used[7] to cleave polymer-bound phosphonate esters to olefinic products.

The Wittig reaction of polymer-bound phosphonium salts has been reviewed[8] and has a key advantage that the phosphine oxide by-product remains bound to the polymer and is thus easily separated from the soluble olefinic product by filtration. As with the Wittig reaction in solution, hydrolysis of the carbon-phosphorus bond has been observed as a minor side reaction.[9]

This report demonstrates that the phosphonium group is sufficiently stable to a range of conditions to allow its use as an alternative traceless linker for solid phase synthesis. In addition, conditions allowing cleavage to products lacking polar functionality by either Wittig or hydrolytic pathways have been developed.

As shown in Scheme 1, the phosphonium salt (**1**) was readily prepared from commercially available[10] polymer-bound triphenylphosphine by the method of Ford.[11] The loading of (**1**) could be assessed either gravimetrically or by bromide analysis of the phosphonium salt. Reduction of the nitro group was achieved with sodium dithionite and was followed by HBr treatment to restore the bromide counter ion. Disappearance of characteristic nitro group absorbances in the FT-IR (KBr) of a small sample of beads allowed the extent of reaction to be monitored. Finally the aniline (**2**) was acylated to anilide (**3**), completion being judged by lack of yellow Schiff's base formation on treatment of a few beads with methanolic 4-nitrobenzaldehyde.

Scheme 1:



a) 2-Nitrobenzyl bromide, DMF, 70 °C, 48 h; b) $Na_2S_2O_4$, EtOH, reflux, 90 min; c) HBr, MeOH, dioxane; d) 4-methoxybenzoyl chloride, pyridine, DCM, 5 h

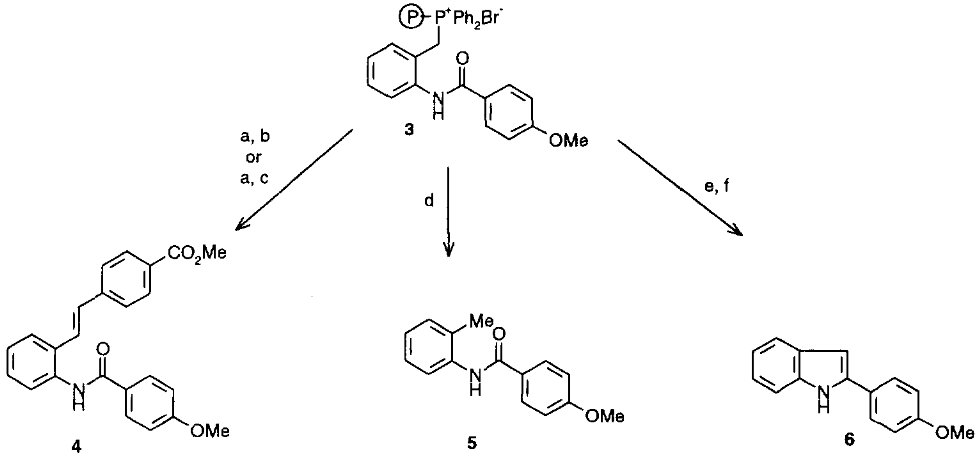
The polymer-bound amide (**3**) can undergo cleavage from the resin by the three pathways shown in Scheme 2.

Conditions developed for the Wittig cleavage of (**3**) to stilbene (**4**), by reaction with sodium methoxide and excess aldehyde in methanol, were found to be suitable for a wide range of substituted benzyl phosphonium salts and aromatic aldehydes. Except in the case of substrates bearing strongly electron-withdrawing substituents, such as (**1**), the use of excess aldehyde suppressed any competing hydrolytic cleavage. Removal of the excess aldehyde component from the soluble product was achieved through formation of either a water soluble hydrazone with Girard's Reagent T[12] or an insoluble imine with aminomethyl resin. The latter was separated along with the polymer-bound triphenylphosphine oxide by-product by simple filtration. A 3:1 *E/Z* mixture of (**4**) was obtained in 82% overall yield.[13]

Hydrolysis of the carbon-phosphonium bond could be made the sole cleavage pathway by omission of aldehyde from the above reaction mixture. Hence, treatment of (**3**) with sodium methoxide gave the toluene derivative (**5**) in 81% yield.[13]

A third cleavage pathway for phosphonium salt (**3**) is available by means of an intramolecular Wittig reaction involving the relatively unreactive amide carbonyl group. This reaction was based on analogous solution chemistry reported by Le Corre,[14] and required strictly anhydrous conditions to avoid hydrolysis. These were achieved by distilling a small quantity of the solvent mixture from the beads prior to addition of base. Cleavage was not observed in the absence of DMF co-solvent which presumably aided solvation and/or swelling of the phosphonium-linked substrate. Under these conditions the 2-substituted indole (**6**) was obtained in 78% yield.[13]

Scheme 2:



a) Methyl 4-formylbenzoate (2 eq), NaOMe (2 eq), MeOH, reflux, 2 h; b) Girard's Reagent T (3 eq), AcOH, 18 h; c) Aminomethyl resin, AcOH, MeOH/dioxane, 18 h; d) NaOMe, MeOH, reflux, 4 h; e) Toluene, DMF, distill; f) KO^tBu, reflux, 45 min

In conclusion, it has been demonstrated that readily available polymer-supported phosphonium salts can be elaborated with reagents including strong acids, organic bases and reducing agents, and can be cleaved under basic conditions to products lacking polar functionality. The phosphonium linkage thus complements many existing linkers both in its acid/base stability profile and its cleavage products. This phosphonium linker is currently being exploited for the solid phase synthesis of combinatorial libraries.

References and notes

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13. Cleavage yields are based on an initial 1.53 meq/g loading of phosphonium salt (**3**) (12.26% bromide).

    Cleavage by Wittig reaction: A suspension of polymer-bound (2-(4-methoxybenzoylamino)benzyl)-triphenylphosphonium bromide (**3**) (500 mg) in dry methanol (15 ml) was treated with 2.0 M sodium methoxide (0.9 ml, 1.8 mmol) immediately followed by methyl 4-formylbenzoate (295 mg, 1.8 mmol). The mixture was heated under reflux for 2 h, cooled and treated with glacial acetic acid (0.5 ml) and (carboxymethyl)trimethylammonium chloride hydrazide (452 mg, 2.7 mmol), then stirred at room temperature overnight. The mixture was filtered through Kieselguhr and washed well with dichloromethane. The filtrate was washed with water (3 x 50 ml) and brine (50 ml), dried (Na$_2$SO$_4$), and evaporated *in vacuo* to leave a 3:1 mixture of *E*- and *Z*-4-methoxy-N-{2-[2-(4-methoxycarbonylphenyl)vinyl]phenyl}benzamides (**4**) as a pale yellow solid (247 mg, 82%). ^{1}H NMR δ (CDCl$_3$) 3.85 (3 H, s, *Z*-isomer), 3.87 (3 H, s, *Z*-isomer), 3.88 (3 H, s, *E*-isomer), 3.92 (3 H, s, *E*-isomer), 6.7-8.3 (Complex m, including: 6.74 (1 H d, *J* = 12.8 Hz, *Z*-isomer), 6.82 (1 H, d, *J* = 12.8 Hz, *Z*-isomer), 6.87 (2 H, d, *J* = 8.5 Hz, *Z*-isomer), 6.98 (2 H, d, *J* = 8.5 Hz, *E*-isomer), 7.07 (1 H, d, *J* = 15.8 Hz, E-isomer), 7.22 (1 H, d, *J* = 15.8 Hz, *E*-isomer), 7.52 (2 H, d, *J* = 8.3 Hz, *E*+*Z*-isomers), 7.87 (d, *J* = 8.9 Hz), and 8.01 (d, *J* = 7.9 Hz)). HRMS (EI): Calculated, 387.1470; Observed, 387.1482.

    Cleavage by hydrolysis: A suspension of polymer-bound (2-(4-methoxybenzoylamino)benzyl)-triphenylphosphonium bromide (**3**) (500 mg) in methanol (15 ml) was treated with 2.0 M sodium methoxide (0.9 ml, 1.8 mmol), and heated under reflux for 4.5 h. The mixture was cooled, filtered through Kieselguhr and the polymer was washed well with dichloromethane. The filtrate was washed with water (2 x 50 ml) and brine (50 ml), then dried (Na$_2$SO$_4$) and evaporated *in vacuo* to leave 4-methoxy-N-(2-methylphenyl)benzamide (**5**) as a white solid (151 mg, 81%). ^{1}H NMR δ (CDCl$_3$) 2.33 (3 H, s), 3.88 (3 H, s), 6.98 (2 H, d, *J* = 8 Hz), 7.10 (1 H, t, *J* = 8 Hz), 7.25 (2 H, m), 7.60 (1 H, br m), 7.86 (2 H, *J* = 8 Hz) and 7.96 (1 H, d, *J* = 8 Hz). HRMS (EI): Calculated, 241.1103; Observed, 241.1111.

    Cleavage by intramolecular Wittig reaction: A suspension of polymer-bound (2-(4-methoxybenzoylamino)benzyl)triphenylphosphonium bromide (**3**) (500 mg) in toluene (25 ml) and DMF (5 ml) was distilled until approx. 5 ml distillate was collected. Potassium t-butoxide (134 mg, 1.2 mmol) was added and the mixture was heated under reflux for 45 min. The mixture was cooled, acidified with 2 N HCl, filtered through Kieselguhr and the polymer was washed well with dichloromethane. The filtrate was washed with water (2 x 50 ml) and brine (50 ml), then was dried (Na$_2$SO$_4$) and evaporated *in vacuo*, to give 2-(4-methoxyphenyl)indole (**6**) (135 mg, 78%). ^{1}H NMR δ (CDCl$_3$) 3.86 (3 H, s), 6.71 (1 H, d, *J* = 3 Hz), 6.98 (2 H, d, *J* = 8 Hz), 7.12 (2 H, m), 7.39 (1 H, d, *J* = 8 Hz), 7.60 (3 H, d, *J* = 8 Hz) and 8.25 (1 H, br s). HRMS (EI): Calculated, 223.0997; Observed, 223.1014.

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