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Note

Palladium cross-coupling reactions on solid support using a new silylated linker

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Dedicated to Professor F. Mathey on the occasion of his 60th birthday

Abstract

The synthesis and the use in palladium cross-coupling reactions of a new silylated stable resin were described. The products have been cleaved from the support using mild conditions and purified with a scavenger ionic resin. A small library of coupling products was obtained. The polymer bond molecules were analyzed by magic angle spinning NMR spectroscopy. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Silylated linker; Palladium; Cross-coupling; HR MAS NMR

1. Introduction

Modification of natural product scaffolds is an attractive strategy for the discovery of new pharmaceutical agents. The combinatorial synthesis of molecular libraries on polymeric supports is a powerful approach for the rapid identification of new compounds that are efficient tools for the study of biological phenomena and new leads for the development of new drugs [1]. The choice of suitable supports and appropriate linkers [2] are of great importance in synthetic sequences.

Silyl derivatives are widely used in synthetic organic chemistry as protecting groups for alcohols, phenols, carboxylic acids, amines, acetylenes and aromatic compounds [3]. Silyl groups are inert to a wide range of synthetic transformations but may be easily removed under selective conditions. To complement existing solution-phase silyl protecting groups, several resin-bound silicon linkers have been developed to enable attachment of alcohols to solid supports. Lithiation of polystyrene, followed by trapping of aryllithium intermediates with dialkyldichlorosilanes [4,5], has been used for preparation of silyl chloride resins where the silicon is directly attached to the polymer backbone. The major drawback of these resins is that they are air and moisture sensitive [5b,5c].

The transition metal-catalyzed cross-coupling reactions, a powerful tool for the formation of carbon–carbon bond, have been widely applied in the synthesis of natural products. Considerable attention has been given to the transition metal-catalyzed cross-coupling reaction mediated by palladium on solid support [6]. Several different types of reactions such as Heck [7], Suzuki [8], and Stille [9] reactions have been reported.

2. Results and discussion

In this paper, we describe the preparation of a new stable silylated polystyrene, Ps–Si$(CH_3)_2$–CH_2–Cl, and its usefulness in the construction of a small library of products obtained via palladium-mediated cross-coupling using miniKan technology [10]. This silylated polymer was similar to Merrifield resin but offered the opportunity to be cleaved under mild conditions.

The reactors were filled up with the commercially available resin (1% divinylbenzene–styrene copolymer),

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scelled and washed with different solvents. Lithiation [4,11] of the copolymer, followed by quenching with chloro(chloromethyl)dimethylsilane in cyclohexane at room temperature provided **2** (Scheme 1). The structure was characterized by IR–FT and HR MAS NMR. The resin **2**, contrary to chlorodimethylsilane resin was stable and could be stored under argon.

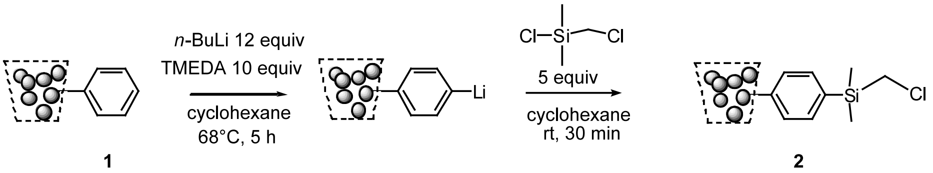
The chloromethyl resin **2** was then esterified with various iodobenzoic acids according to previously optimized conditions [12]. The cesium carboxylate was first prepared, added to **2** in DMF and the mixture was shaken at 50° C during 24 h (Scheme 2) [13]. A complete conversion in supported aromatic iodo esters **3**, **4**, **5** was observed by FT–IR: disappearance of the C–Cl band (603 cm^{-1}) and by solid-phase HR MAS ^{1}H-NMR: shift of CH_2 signal from 3.05 to 4.2 ppm. To confirm this conversion, the resin was cleaved by TFA in THF and iodo benzoic methyl ester was isolated in 80% yield after chromatography.

We next examined the palladium-catalyzed cross-coupling reaction with these supported aryliodides. The Heck reactions with ethyl acrylate were carried out in DMF under argon using $Pd(OAc)_2/PPh_3$ catalyst and an excess of olefin and base. The conversion was complete in 16 h at 80 °C as shown by HR MAS ^{1}H-NMR and FT–IR spectral analyses (Scheme 3) [14].

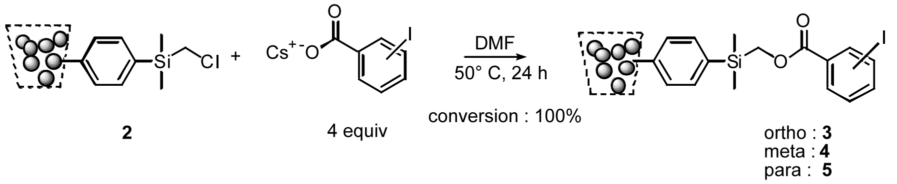
In the same way, the supported aryliodides were coupled with trimethylsilylacetylene in THF under argon in the presence of catalytic CuI (Sonogashira couplings). After 16 h at reflux of THF, complete conversion was observed [15].

In a third series of experiment, we tested these supported aryliodides in the Suzuki coupling using typical solution phase Suzuki coupling: excess of boronic acid, K_2CO_3 as base, at reflux of DMF. Under these conditions, again we observed a completed conversion (Scheme 3) [16]. All conversions were determined by HR MAS ^{1}H-NMR.

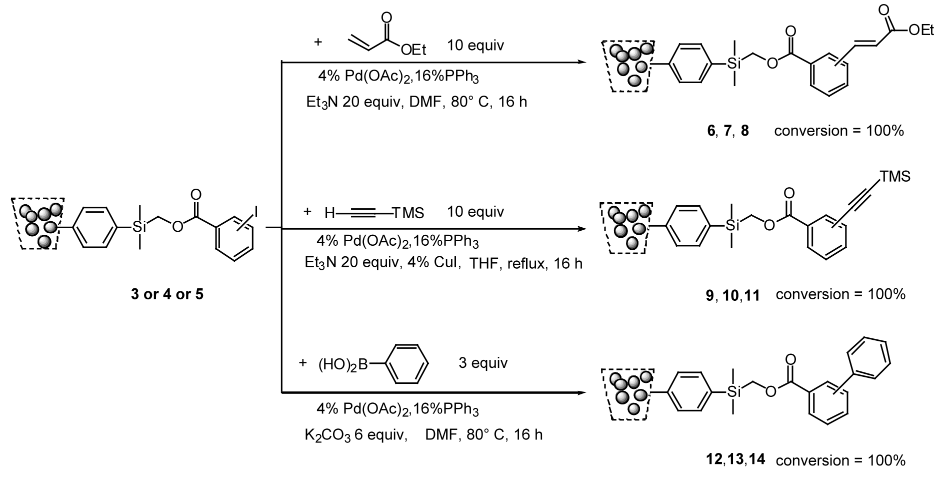
To probe the efficiency of couplings, esters, after separation, were cleaved with TBAF in THF. However due to small quantities of resins in miniKan, excess of TBAF was difficult to eliminate. Therefore an Am-



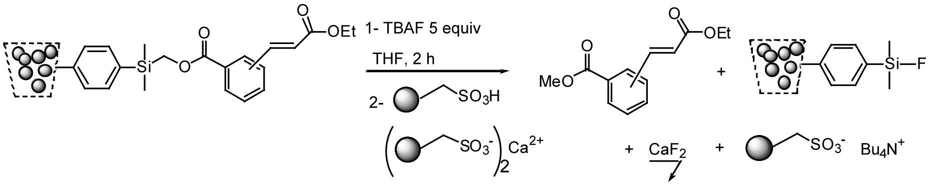
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

berlyst A-15 and its calcium salt were used to purify the mixture [17] as presented in Scheme 4. By simple filtration and solvent evaporation, the methyl ester was obtained in 70% yield and in high purity proved by ^{1}H- and ^{13}C-NMR.

3. Conclusion

In this paper, we have shown that a variety of aryliodides immobilized on a new silylated resin can be subjected to preparatively useful coupling reactions. A mini library has been developed and automatization could be envisaged with miniKan technology. This technology is presently being used in our laboratories to create libraries of diversely functionalized molecules with biological properties.

Acknowledgements

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[11] Polystyrene 1% divinylbenzene copolymer beads, 200–400 mesh (2.5 g) was swollen in dry cyclohexane (5 ml). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (3.8 ml, 10 equivalents, 25 mmol) was added followed by a 2.5 M solution of *n*-butyllithium in hexane (11 ml, 11 equivalents, 27 mmol). The suspension was gently shaken at 68 °C during 5 h until the resin turned dark red. The resin was allowed to settle and was washed three times with dry cyclohexane (15 ml) under argon. The red resin was then swollen in dry cyclohexane (10 ml) and chloro(chloromethyl)dimethylsilane (3.3 ml, 10 equivalents, 25 mmol) was added dropwise. The resin turned white and was gently shaken for 30 min and filtered off and washed with DMF (3×30 ml), DMF–water (2×30 ml), THF (2×30 ml), THF–water (2×30 ml), THF (3×30 ml) MeOH (30 ml) and alternatively three times with CH_2Cl_2–MeOH (30 ml). The resin (3 g) was dried in vacuo for 5 h. ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.35 (s, 6H) 3.05 (s, 2H). ^{13}C-NMR (DMF D7, 100 MHz): $-4{,}30$. IR (KBr) cm^{-1}: 1411, 1249 ν_{Si-CH_3}, 838, 811 $\nu_{Si-(CH_3)_2}$, 603 ν_{C-Cl}.

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[13] General procedure for the attachment of iodobenzoic acids to chloromethyl silyl resin:

A solution of iodobenzoic acid (350 mg, four equivalents, 1.4 mmol, M = 248.02) in methanol (7 ml) and water (0.7 ml) was titrated to pH 7 with a 20% aqueous solution of cesium carbonate ($\approx$ 3 ml). The mixture was evaporated to dryness and DMF (2 ml) was added. After evaporation to dryness, a second portion of DMF (2 ml) was added and evaporated. In the dry carboxylic acid cesium salt the resin (350 mg, 0.35 mmol, $\tau = 1$) was added followed by DMF (6 ml). The suspension was gently shaken at 50 °C during 24 h. The resin was filtered off and washed with DMF (3 × 30 ml), DMF–water (2 × 30 ml), THF (2 × 30 ml), THF–water (2 × 30 ml), THF (3 × 30 ml) MeOH (30 ml) and alternatively three times with CH$_2$Cl$_2$ MeOH (30 ml). The resin was dried in vacuo for 5 h.

Solid phase (dimethyl-phenyl-silanyl)-methyl-2-iodobenzoic ester (**3**): according to general procedure for the attachment of iodobenzoic acids to chloromethyl silyl resin (use of 2-iodobenzoic acid), 420 mg of resin were isolated ($\tau = 1$ mmol g^{-1})). ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.37 (s, 6H), 4.2 (s, CH$_2$), 7.12 (s, Harom), 7.38 (s, Harom), 7.66 (s, Harom), 7.98 (s, Harom). IR (KBr) cm^{-1}: 1726 $\nu_{C=O}$, 1411, 1248 ν_{Si-CH_3}.

4: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.37 (s, 6H), 4.21 (s, CH$_2$), 7.30 (s, 1Harom), 7.97 (s, 2Harom), 8.34 (s, 1Harom). IR (KBr) cm^{-1}: 1721 $\nu_{C=O}$, 1411, 1248 ν_{Si-CH_3}.

5: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.37 (s, 6H), 4.19 (s, CH$_2$), 7.72 (1s, 2Harom), 7.82 (1s, 2Harom). IR (KBr) cm^{-1}: 1730 $\nu_{C=O}$, 1411, 1248 ν_{Si-CH_3}.

[14] General procedure for the solid support Heck couplings: the iodate resin in miniKan (0.6 mmol, $\tau = 1$ mmol g^{-1}) was swollen in degassed DMF (5 ml per miniKan). Ethyl acrylate (650 µl, 10 equivalents), palladium acetate (5.4 mg, 0.024 mmol), triphenylphosphine (25.1 mg, 0.096 mmol) and triethylamine (1.6 ml, 12 mmol) were added. The suspension was shaken at 80 °C during 16 h. The miniKans were filtered off and washed with DMF (3 × 50 ml), DMF–water (2 × 50 ml), THF (2 × 50 ml), THF–water (2 × 50 ml), THF (3 × 50 ml), MeOH (50 ml and alternatively with CH$_2$Cl$_2$–MeOH (50 ml). The miniKans were dried in vacuo for 5 h.

6: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.37 (s, 6H), 1.5 (s, CH$_3$), 4.20 (s, Si–$\mathbf{CH_2}$), 4.50 (s, $\mathbf{CH_2}$–CH$_3$), 6.75 (s, CH=), 7.55 (s, 1Harom), 7.65 (s, 1Harom), 7.90 (s, 1Harom), 8.05 (s, 1Harom), 8.65 (s, CH=). IR (KBr) cm^{-1}: 1721 $\nu_{C=O}$, 1640 $\nu_{C=C}$, 1415, 1248 ν_{Si-CH_3}.

7: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.35 (s, 6 H), 1.25 (s, CH$_3$), 4.20 (s, $\mathbf{CH_2}$–CH$_3$), 4.23 (s, Si–$\mathbf{CH_2}$), 6.65 (s, CH=), 7.20 (s, 1Harom), 7.75 (s, 1Harom), 7.94 (s, 1Harom), 7.97 (s, 1Harom), 8.32 (s, CH=). ^{13}C-NMR (DMF D7, 100 MHz): 165 (CO), 148 (CH=), 143, 142, 138, 131, 130 (Carom), 58 ($\mathbf{CH_2}$–CH$_3$), 57 (Si–$\mathbf{CH_2}$), 15 (CH$_3$), −4.2 (Si–$\mathbf{CH_3}$). IR (KBr) cm^{-1}: 1718 $\nu_{C=O}$, 1641 $\nu_{C=C}$, 1415, 1249 ν_{Si-CH_3}.

8: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.35 (s, 6H), 1.27 (s, CH$_3$), 4.20 (s, $\mathbf{CH_2}$–CH$_3$), 4.23 (s, Si–$\mathbf{CH_2}$), 6.70 (s, CH=), 7.70 (s, CH=), 7.72, 7.95 (2s, 4Harom). IR (KBr) cm^{-1}: 1717 $\nu_{C=O}$, 1639 $\nu_{C=C}$, 1412, 1249 ν_{Si-CH_3}.

[15] General procedure for the solid support Sonogashira couplings: the iodate resin in miniKan (0.6 mmol, $\tau = 1$ mmol g^{-1}) was swollen in degassed THF (5 ml per miniKan). Trimethylsilylacetylene (850 µl, 10 equivalents), palladium acetate (5.4 mg, 0.024 mmol), triphenylphosphine (25.1 mg, 0.096 mmol), copper iodide (4.5 mg, 0.024 mmol) and triethylamine (1.6 ml, 12 mmol) were added. The suspension was shaken at reflux during 16 h. The miniKan were filtered off and washed with DMF (3 × 50 ml), DMF–water (2 × 50 ml), THF (2 × 50 ml), THF–water (2 × 50 ml), THF (3 × 50 ml), MeOH (50 ml and alternatively CH$_2$Cl$_2$, MeOH (50 ml). The miniKans were dried in vacuo for 5 h.

9: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.22 (s, Si–($\mathbf{CH_3}$)$_3$), 0.32 (Si–CH$_3$), 4.19 (Si–$\mathbf{CH_2}$), 7.30, 7.40, 7.45, 7.70 (4s, 4 Harom). IR (KBr) cm^{-1}: 2159 $\nu_{C\equiv C}$, 1720 $\nu_{C=O}$, 1250 ν_{Si-CH_3}.

10: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.22 (s, Si–($\mathbf{CH_3}$)$_3$), 0.32 (Si–CH$_3$), 4.20 (Si–$\mathbf{CH_2}$), 7.50, 7.70, 8.03, 8.12 (4s, 4Harom). IR (KBr) cm^{-1}: 2158 $\nu_{C\equiv C}$, 1723 $\nu_{C=O}$, 1250 ν_{Si-CH_3}.

11: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.22 (s, Si–($\mathbf{CH_3}$)$_3$), 0.32 (Si–CH$_3$), 4.19 (Si–$\mathbf{CH_2}$), 7.50, 8.00 (2s, 4Harom). IR (KBr) cm^{-1}: 2160 $\nu_{C\equiv C}$, 1718 $\nu_{C=O}$, 1250 ν_{Si-CH_3}.

[16] General procedure for the solid support Suzuki couplings: the iodate resin in miniKan (0.6 mmol, $\tau = 1$ mmol g^{-1}) was swollen in degassed DMF (5 ml per miniKan). Phenyl boronic acid (220 mg, three equivalents), palladium acetate (5.4 mg, 0.024 mmol), triphenylphosphine (25.1 mg, 0.096 mmol) and potassium carbonate (500 mg, 3.6 mmol) were added. The suspension was shaken at 80 °C during 16 h. The miniKans were filtered off and washed with DMF (3 × 50 ml), DMF–water (2 × 50 ml), THF (2 × 50 ml), THF–water (2 × 50 ml), THF (3 × 50 ml), MeOH (50 ml and alternatively CH$_2$Cl$_2$, MeOH (50 ml). The miniKans were dried in vacuo for 5 h.

12: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.37 (Si–$\mathbf{CH_3}$), 4.19 (Si–$\mathbf{CH_2}$), 7.40 (s, 2Harom), 7.4–7.55 (m, 4Harom), 7.65 (s, 1Harom). IR (KBr) cm^{-1}: 1718 $\nu_{C=O}$, 1249 ν_{Si-CH_3}.

13: ^{1}H-NMR (DMF D7, 400 MHz): δ (ppm) 0.37 (Si–$\mathbf{CH_3}$), 4.19 (Si–$\mathbf{CH_2}$), 7.40 (s, 2Harom), 7.50 (s, 1Harom), 7.65 (s, 1Harom), 7.85, 8.01 (2s, 2Harom), 8.30 (s, 1Harom). IR (KBr) cm^{-1}: 1718 $\nu_{C=O}$, 1249 ν_{Si-CH_3}.

14: 0.37 (Si–CH$_3$), 4.19 (Si–CH$_2$), 7.40, 7.65, 7.70, 8.10 (s, Harom). IR (KBr) cm^{-1}: 1717 $\nu_{C=O}$, 1249 ν_{Si-CH_3}.

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