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Synthesis of Polymer-Bound 4-Acetoxy-3-phenylbenzaldehyde Derivatives:

Applications in Solid-Phase Organic Synthesis

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Abstract

Aminomethyl polystyrene resin was reacted with 4-(5'-formyl-2'-hydroxyphenyl)benzoic acid and 4-(5'-formyl-2'-hydroxyphenyl)phenyl propionic acid, respectively, in the presence of 1-hydroxybenzotriazole and 1,3-diisopropylcarbodiimide to yield polymer-bound benzaldehydes. The phenolic group in resins was acetylated with acetic anhydride to afford two polymer-bound 4-acetoxybenzaldehydes. The reductive amination of polymer-bound linkers by amines and sodium triacetoxyborohydride, followed by sulfonylation with alkyl or arylsulfonyl chloride derivatives in the presence of pyridine and the cleavage with TFA/DCM, produced pure sulfonamides.

Solid-phase organic synthesis has emerged as a powerful tool to generate large molecular libraries¹⁻³ of small-sized molecules and to accelerate lead discovery and optimization processes. The challenge now is to extend the ability of solid-phase chemistry to generate a large number of structurally diversified compounds by developing suitable polymer-bound reagents^{4,5} that accommodate the synthesis of various compounds.

The reagents have to be attached to the polymer through a linker. Linkers that can generate different compounds depending on the attached compounds and the cleavage conditions are needed. A number of polymer-bound linkers have been used for the synthesis of different compounds.⁵⁻²⁹ In some cases, the purification of final products is still needed, because of the instability of polymer-bound linkers in different reaction conditions and/or the leakage of different materials upon cleavage. Therefore, the polymer-bound linkers that have application in producing pure final products are preferred. Stable polymer-bound linkers are needed that provide the concomitant cleavage of pure and various products and removal of the linker group without any loss in overall synthetic efficiency. Furthermore, for the synthesis of diverse number of compounds, such as organosulfur and organophosphorus compounds, polymer-bound linkers have not been developed extensively.

To explore further the synthetic utility of the polymer-bound linkers as tools for the synthesis of diverse number of compounds without the need of purification in the final cleavage step, two new polymer-bound linkers of *p*-acetoxybenzaldehyde, **1a** and **1b**, were synthesized (Figure 1).

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Because of the proximity of the amino group and *p*-acetoxy group in the previous reported polymer-bound linkers of *p*-acetoxybenzyl alcohol^{20,23,24}, the intramolecular reactions caused uncontrolled partial release of some intermediates before further modifications on attached moieties (**X**) (Scheme 1). Therefore, the yield of final products was lower than expected.

Polymer-bound *p*-acetoxybenzaldehydes **1a** and **1b** offered several advantages compared to other polymer-bound linkers reported by us and others.^{20,23,24} First, a large separation between the nitrogen atom in amide and *p*-acetoxy group was introduced in new polymer-bound linkers **1a** and **1b**. The presence of the nitrogen atom in amide form and the large distance between amide bond and *p*-acetoxy group minimized the intramolecular reaction between these functional groups. The polymer-bound intermediates were stable even in basic conditions. Second, **1a** and **1b** were designed to produce final products without the need for purification. The final products were synthesized in a short period, high yields, and parallel format, and were easily separated from the resin-bound linkers. Finally, **1a** and **1b** were stable in basic conditions (e.g., pyridine). This allows the potential use of **1a** and **1b** for the synthesis of diverse classes of compounds by converting them to polymer-bound amines through reductive amination and further substitution of amino functional groups. To demonstrate this, their application in solid-phase organic synthesis of sulfonamides is shown here. Presumably, **1a** and **1b** can be reduced to polymer-bound benzyl alcohols and then be used for the synthesis of monophosphorylated compounds as shown previously for other polymer-bound linkers of *p*-acetoxybenzyl alcohol.²¹⁻²⁵

For the synthesis of polymer-bound *p*-acetoxybenzaldehydes **1a** and **1b**, building block linkers, 4-(5'-formyl-2'-hydroxyphenyl)benzoic acid (**5a**) and 4-(5'-formyl-2'-hydroxyphenyl)phenyl propionic acid (**5b**), were required for the attachment to aminomethyl polystyrene resin. The reaction of 3-bromo-4-hydroxybenzaldehyde (**4**) in toluene/ethanol/water with 4-(4,4,5,5-tetramethyl-1,3,2-bioxaborolan-2-yl)benzoic acid (**3a**) and [4-(2-carboxyethyl)phenyl]boronic acid (**3b**), respectively, in the presence of tetrakis(triphenylphosphine)palladium (Pd (Ph₃P)₄) at 110 °C for 13 h afforded (**5a**, 83%) and (**5b**, 95%) (Scheme 2). Compound **3a** was synthesized quantitatively by the reaction between 2,3-dimethyl-2,3-butanediol (pinacol) and 4-carboxylphenylboronic acid (**2**) in THF/toluene (Scheme 2). Although compound **2** can be used directly in reaction with **4**, we used protected form of boronic acid **3a**. It appears that the protection of boronic acid is not essential, since **5b** was produced from unprotected **3b** in a slightly higher yield when compared to that of **5a** from protected **3a**.

Building block linkers **5a** and **5b** were used for the synthesis of **1a** and **1b**, respectively (Scheme 3). The reaction of aminomethyl polystyrene resin **6** with **5a** and **5b**, respectively, in the presence of 1-hydroxybenzotriazole (HOBt) and 1,3-diisopropylcarbodiimide (DIC) afforded **7a-b**. Polymer-bound *p*-acetoxybenzaldehydes, **1a-b**, were synthesized by the reaction of **7a-b** with acetic anhydride in the presence of pyridine (Scheme 3).

We investigated whether developed polymer-bound linkers can have potential application for the synthesis of sulfonamides. Sulfonamides are currently used as therapeutic agents, such as sulfa antibiotics (e.g., sulfathiazole) or serotonin antagonists (e.g., antimigraine Sumatriptan).³⁰ Isoquinoline sulfonamides inhibit protein kinases by competing with ATP.³¹⁻³³ Although sulfonamides can be synthesized through solution-phase methods, the synthesis of large library of sulfonamides using these strategies is cumbersome, because a large number of final products need to be purified. Several solid-phase routes have been reported for the synthesis of sulfonamides.^{34,35} We examined polymer-bound linkers of *p*-acetoxybenzaldehyde (**1a-b**) for the synthesis of sulfonamides to demonstrate their general application.

The solid-phase synthetic strategy of sulfonamides consisted of three steps (Scheme 4): reductive amination, sulfonylation, and cleavage. The reductive amination of a polymer-bound aldehydes **1a-b** by amines (e.g., aniline, 4-chloroaniline, benzylamine, 4-methoxybenzylamine,) and sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$) afforded **9-12a** and **9-12b**. Sulfonylation of resin-bound amines **9-12a** and **9-12b** with alkyl or arylsulfonyl chloride derivatives (e.g., *p*-toluenesulfonyl chloride, 3,5-dimethoxybenzene-1-sulfonyl chloride, 3-nitrobenzenesulfonyl chloride) in the presence of pyridine gave polymer-bound sulfonamides **13-24a** and **13-24b**. The sulfonamide remained bound to the polymer-bound linker under basic conditions. The activation step by hydrolysis of the acetyl group and cleavage of the products from the resins in TFA/DCM/ H_2O (74:24:2 v/v/v) produced pure sulfonamides **26-37** (>98%) (Scheme 4). In total, by using different combinations of amines and sulfonyl chlorides, 12 compounds were synthesized using both polymer-bound linkers (overall yield 60-83% calculated from **1a-b**). Compounds **27**, **30**, **33**, and **36** are novel compounds.

The cleavage mechanism of final sulfonamides from **13-24a** and **13-24b** is shown in Scheme 4. The multi-step cleavage mechanism is shown in one step here for simple demonstration. The linkers remained covalently bound on the resins using both polymer-bound linkers, which facilitated the separation of the final products by filtration.

Figure 2 shows the chemical structures of the synthesized compounds. The final products were characterized by nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR), and high-resolution time-of-flight electrospray mass spectrometry.

Products were compared for yield and purity. There were no significant differences in the purity of the final products using resin-bound linkers **1a** and **1b** (>98%), but most compounds were produced from **1a** in higher yields than those from **1b** (Table 1). The compounds did not need any purification (>98% pure) compared with the previously reported solid-phase methods for the synthesis of sulfonamides,^{34,35} and were produced in comparable or higher yields.

In conclusion, two stable polymer-bound linkers were synthesized and used for the solid-phase synthesis of sulfonamides. The amines and sulfonyl chlorides were mixed with the polymer-bound linkers, respectively, and were thereby “captured” as immobilized compounds. Washing the support guaranteed that no unreacted starting amines or sulfonyl chlorides remained. In the final cleavage reaction, the linkers remained covalently bound on the resins, which facilitated the separation of the final products by filtration. This solid-phase strategy allowed the synthesis of sulfonamides in a short synthetic route without the need for purification of intermediates and final products. Furthermore, this strategy offered the advantages of facile isolation and recovery of pure final products. These polymer-bound linkers can be used for solid-phase preparation of other biologically important compounds.

Experimental Section

As a representative example, resin **1a** (1.62 g, 0.78 mmol/g) was swelled in 1,2-dichloroethane (30 mL) and was shaken at room temperature for 15 min. Aniline (0.6 mL, 6.4 mmol) was added to the swelled resin. The mixture was shaken for 1 h at room temperature. $\text{NaBH}(\text{OAc})_3$ (1.35 g, 6.4 mmol) was added to the reaction mixture. After 6 h shaking at room temperature, the resin was collected by filtration and washed with water (2×30 mL), DCM (2×30 mL), and MeOH (2×30 mL), respectively, and dried under vacuum to give **9a** (1.71 g, 94%, 0.70 mmol/g). Polymer-bound aniline **9a** (550 mg, 0.70 mmol/g) was swelled in cold dry pyridine (30 mL). To the swelled resin *p*-toluenesulfonyl chloride (1.0 g, 5.26 mmol) was added and the reaction was stirred at room temperature for 6 h. The resin was washed with water (2×30 mL), DCM (2×30 mL) and MeOH (2×30 mL), and dried under vacuum for 24 h to give **13a** (606 mg, 95%, 0.60 mmol/g). Polymer-bound sulfonamide **13a** (606 mg, 0.60

mmol/g) was suspended in TFA/DCM/H₂O (74:24:2 v/v/v, 5 mL). After 30 min shaking of the mixture at room temperature, the resin was collected by filtration and washed with DCM (5 mL), THF (5 mL), and MeOH (5 mL). The filtrate was evaporated at room temperature and the residue was washed with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). The organic phase was dried with anhydrous sodium sulfate and evaporated to afford pure 4-methyl-*N*-phenylbenzenesulfonamide (**26**, 84 mg, 94%; overall yield calculated from **1a**, 83%). ¹H NMR (CDCl₃, 400 MHz, δ ppm): 7.70 (d, *J* = 8.30 Hz, 2H), 7.30–7.21 (m, 4H), 7.19 (br s, 1H), 7.14–7.06 (m, 3H), 2.37 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz, δ ppm): 144.3, 137.0, 136.4, 130.1, 129.7, 127.7, 125.6, 121.9, 22.0; HR-MS (ESI-TOF) (*m/z*) for C₁₃H₁₃NO₂S: calcd, 247.0667; found, 248.2760 [M + H]⁺.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Polymer-bound linkers of *p*-acetoxybenzaldehyde, **1a** and **1b**.

Figure 2.
Structures of Synthesized Sulfonamides.

Scheme 1.

The intramolecular reaction in polymer-bound intermediates derived from polymer-bound *p*-acetoxybenzyl alcohol reduces the efficiency in solid-phase synthesis, because of the partial loss and release of some of the unmodified intermediates.

Scheme 2.
Synthesis of Building Block Linkers **5a** and **5b**.

Scheme 3.
Synthesis of Solid-Phase Polymer-Bound Linkers of 4-Acetoxy-3-phenylbenzaldehyde (**1a-b**).

Scheme 4.
Synthesis of Sulfonamides.

Table 1
Overall Isolated Yields and Final Cleavage Yields of Products for Sulfonamides (**26-37**)

No.	Overall yield (%) calcd from 1a	Overall yield (%) calcd from 1b	Final Cleavage Yield (%) from 13-24a	Final Cleavage Yield (%) from 13-24b
26	83	72	94	89
27	78	73	91	86
28	80	74	96	89
29	82	76	88	93
30	81	74	89	89
31	72	60	84	78
32	70	78	85	90
33	77	74	90	87
34	62	74	80	89
35	67	74	88	88
36	76	79	95	90
37	67	72	88	86