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Polymer-supported *N*-benzyl- and *N*-benzhydryl-2-nitrobenzenesulfonamides as alternative to aldehyde linkers

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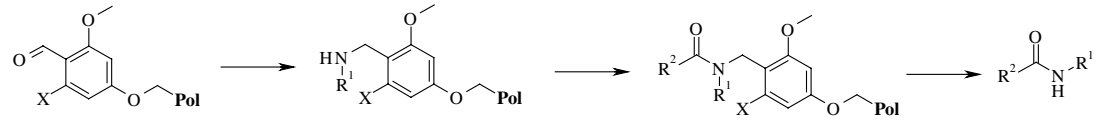
Abstract—Polymer-supported *N*-benzyl- and *N*-benzhydryl-2-nitrobenzenesulfonamides **1** were *N*-alkylated using three different routes: via Fukuyama reaction with alcohols, by *N*-alkylation with electrophiles, and by Michael addition reaction with α,β-unsaturated carbonyl compounds. The *N*-alkylated products were obtained in excellent purity and high yield. The 2-nitrobenzenesulfonyl (Nos) group was then cleaved to yield polymer-supported *N*-alkylated benzylamines and benzhydrylamines. *N*-alkylation of polymer-supported 2-nitrobenzenesulfonamide linkers **1** described herein represents an alternative route to reductive amination of aldehyde linkers.

1. Introduction

Polymer-supported aldehyde linkers have become established starting synthons for solid-phase synthesis of diverse classes of nitrogen-containing compounds. Backbone amide linker (BAL) was originally developed for the synthesis of peptides immobilized via a peptide amide nitrogen.[1] Aldehyde linkers including the AMEBA (Acid sensitive MEthoxyBenzAldehyde)[2] and MALDRE (2-Methoxy-4-benzyloxy-polystyrene ALDehyde REsin)[3] linkers were used for the synthesis of secondary amides,[1–5] ureas,[2,5] carbamates,[2] sulfonamides,[2,5] and nitrogen-containing heterocyclic compounds.[6,7] Key intermediates, the resin-bound *N*-alkylated (di- and tri-alkoxy)benzylamines are typically prepared from the corresponding aldehyde resins and amines by reductive amination (Scheme 1). Because of the immense number of available amines, this approach is a very valuable tool for combinatorial solid-phase synthesis. The same kind of resin-bound *N*-alkyl-(di- and tri-alkoxy)benzylamines can be approached by *N*-alkylation of the polymer-supported *N*-(di- and tri-alkoxy)benzyl-2-nitro-benzenesulfonamides, followed by cleavage of the Nos group. In addition, *N*-alkylated benzhydrylamines are prepared in an analogous fashion.

The synthesis of Nos linkers **1** is simple and straightforward. Aminomethyl PS/DVB resin (Advanced ChemTech, 1.2 mmol/g) was acylated with 5-[4-(9-fluorenylmethyloxycarbonyl)amino-3,5-dimethoxyphenoxy]-pentanoic acid (PAL linker).[8] Cleavage with 10% TFA in DCM for 30 min yielded Fmoc-NH_2 in 93% yield (calculated from the HPLC traces at 300 nm with respect to a standard). The Fmoc group was cleaved and the amino group reacted with 2-nitrobenzenesulfonyl chloride to yield resin **1a**. The resin **1b** was prepared from the



Scheme 1. The aldehyde linker for the synthesis of amides.

Keywords: Solid-phase synthesis; Linker; 2-Nitrobenzenesulfonamides; Benzylamine.
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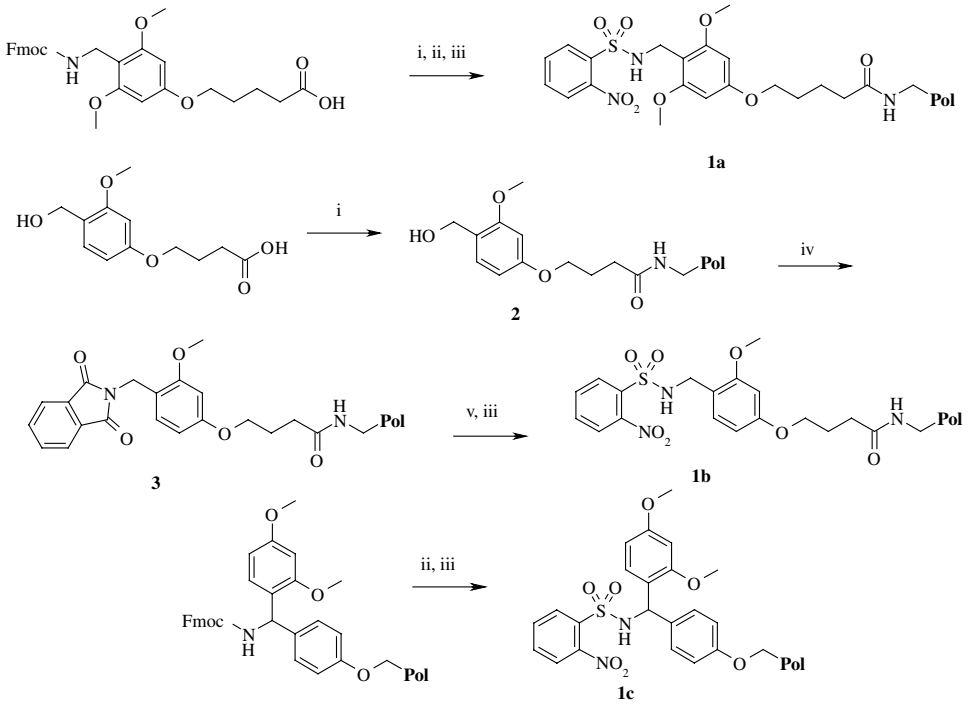


Scheme 2. Synthesis of 2-nitrobenzenesulfonamide resins. Reagents and conditions: (i) aminomethyl PS/DVB resin, DIC, HOBt, DMF, 20 °C, overnight; (ii) 20% piperidine, DMF, 20 °C, 20 min; (iii) Nos-Cl, 2,6-lutidine, DCM, 20 °C, overnight; (iv) phthalimide, PPh_3, DIAD, anhydrous THF, 20 °C, overnight; (v) 5% hydrazine hydrate, THF–MeOH (1:1), 20 °C, overnight.

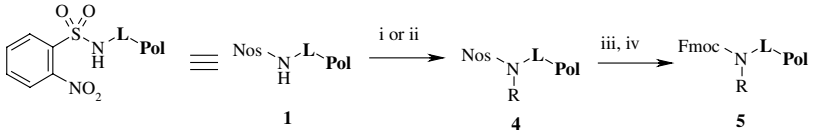
aminomethyl PS/DVB resin by acylation with 4-(4-hydroxymethyl-3-methoxyphenoxy)-butyric acid (HMPB linker)[9] via DIC/HOBt activation. Acylation of a sample with Fmoc-Ser(*t*-Bu)-OH (HOBt, DIC, DMAP) and subsequent cleavage with TFA/DCM yielded 91% of the expected product. The HMPB resin **2** was reacted with phthalimide under Mitsunobu conditions using the published protocol[10] to yield resin **3**. The phthalimide group was cleaved by hydrazine hydrate, and the resin-bound benzylamine reacted with 2-nitrobenzenesulfonyl chloride (resin **1b**). Resin **1c** was prepared from commercially available polymer supported Rink linker.[11] The 2-nitrobenzenesulfonamide resins **1** were used as a starting material for the *N*-alkylation.[12] The resin-bound linkers differ by acid lability, the **1b** linker being the most acid stabile (Scheme 2).

Fukuyama synthesis of secondary amines[13] was used as the first *N*-alkylation procedure. The Fukuyama reaction has been successfully applied to solid-phase synthesis of amines on numerous occasions.[14–22] Fukuyama *N*-alkylation proceeded smoothly with a range of diverse alcohols and produced the resin **4**. An alternative route applied for the introduction of the *N*-alkyl substitution was alkylation by an electrophile in the presence of a base. BEMP provided superior results with respect to product purity (Scheme 3).

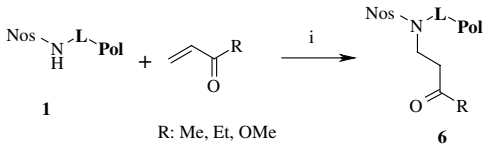
Michael addition was used to install the *N*-substituent by, α,β-unsaturated carbonyl compounds (product **6**). The reaction was carried out in anhydrous THF with catalytic amount of the BEMP as a base (Scheme 4).

N-Alkylated products were cleaved from the resin by TFA/methylene chloride mixture, 30 min 10% TFA for linkers **1a** and **1c** and 60 min in 50% TFA for linker **1b**. Partial decomposition of the product cleaved from the linker **1b** was observed. The Nos protecting group was cleaved by DMF solution of 2-mercaptoethanol in the presence of DBU. In order to evaluate the yield of the product, the resin-bound *N*-alkyl benzylamines were reacted with Fmoc-ONSu and the product cleaved by TFA/methylene chloride mixture. The analytical results are summarized in Table 1.

In summary, the polymer-supported 2-nitrobenzenesulfonamide linkers **1** offer an alternative route to polymer-supported *N*-alkylated benzylamines, which



Scheme 3. Alkylation of 2-nitrobenzenesulfonamide resin. Reagents and conditions: (i) R-OH, PPh_3, DEAD, anhydrous THF, 20 °C, overnight; (ii) R-Br, BEMP, anhydrous THF, 20 °C, overnight; (iii) 2-mercaptoethanol, DBU, DMF, 20 °C, 30 min; (iv) Fmoc-ONSu, DCM, 30 min.



Scheme 4. Michael addition reaction with 2-nitrobenzenesulfonamide resin. Reagents and conditions: (i) 1% BEMP, anhydrous THF, 20 °C, overnight.

Table 1. *N*-Alkylation of polymer-supported *N*-benzyl-2-nitro-benzenesulfonamide **1a**[a]

Entry	Reagent	t_R[b]	Purity (%)[c]	t_R[d]	Yield (%)[e]
1	Methyl alcohol	2.50	99	6.38	92
2	Benzyl alcohol	5.95	94	8.28	90
3	Methoxyethanol	3.17	89	6.52	87
4	2-(Phenylthio)ethanol	7.03	95	9.03	71
5	3-Hydroxymethylpyridine	2.10	91	4.48	79
6	4-(*tert*-Butyl)benzylbromide	8.22	98	10.05	75
7	Ethylbromoacetate	4.02	95	7.10	74
8	Vinyl methyl ketone	3.13	86	6.40	71
9	Vinyl ethyl ketone	4.11	88	7.10	80
10	Methyl acrylate	4.08	95	6.86	83

[a] All products afforded expected diagnostic ion in mass spectra.
[b] Retention time of the Nos-derivatives (C18 X-terra 30 × 3 mm column, 1.4 mL/min, gradient 0–60% from water with 0.1% TFA to MeCN in 10 min).
[c] Peak area on analytical HPLC traces of the Nos-derivative at 220 nm.
[d] Retention time of the Fmoc-derivatives.
[e] Yield of cleaved Fmoc-derivative, calculated from the integrated peak area on analytical HPLC traces at 300 nm.

were shown to be a very useful class of resin-bound intermediates. *N*-Alkylation reactions proceed under mild conditions, they are amenable to manual parallel synthesis, and the yield and purity of products are excellent. Whereas the aldehyde linkers use amines as building blocks, the present linkers takes advantage of alcohols, electrophiles, and α,β-unsaturated carbonyl compounds.

2. General procedure

Resin **1** (100 mg) in a 3 mL polypropylene disposable reaction vessel (www.torviq.com) was washed three times with anhydrous THF.

Reaction with alcohols: The reaction vessel was charged with 2 mL of 0.25 M PPh_3 (131 mg) solution. Alcohol (0.5 mmol) was added and the reaction vessel was cooled in a freezer for 30 min. DEAD (0.5 mmol, 40% solution in toluene, 226 μL) was added and the resin slurry was shaken at ambient temperature overnight.

Alkylation with alkylbromides: The reaction vessel was charged with 2 mL of 0.25 M alkylbromide solution. BEMP (0.5 mmol, 144 μL) was added and the resin slurry was shaken at ambient temperature overnight.

Michael addition reaction: The reaction vessel was charged with 2 mL of 0.25 M, α,β-unsaturated carbonyl compound solution. BEMP (0.05 mmol, 14 μL) was added and the resin slurry was shaken at ambient temperature overnight.

The resin was washed three times with THF and DCM.

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