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An alternative method for the preparation of resin-bound secondary amines

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Abstract—Difficulties encountered in the synthesis of resin-bound secondary amines attached via an acid-labile linker encouraged us to employ an alternative approach. A one-pot, scalable procedure for the synthesis of Fmoc-protected, amine/linker constructs is reported. These compounds can be efficiently coupled to a solid support and be used in the synthesis of carboxamides and sulfonamides. The advantages of the method are the elimination of problems associated with variability of alkoxybenzaldehyde resins, minimization of difficulties encountered in solid-phase reductive aminations, and a means for quantifying the resin loading of the secondary amine. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Polymers supporting alkoxybenzaldehyde linkers have become standard tools for the solid-phase synthesis of *N*-substituted carboxamides and sulfonamides.[1,2] Treatment of these supports with primary amines provides intermediate imines that are reducible to secondary amines. Reaction with activated acylating and sulfonylating agents yields carboxamides and sulfonamides that are released upon exposure to acidic conditions.

2. Results and discussion

While in the process of developing a method for the high-throughput synthesis of various amide containing libraries, our intention was to perform a reductive amination directly on an alkoxybenzaldehyde resin, then couple a scaffold to provide a tertiary amide. The scaffold would be further derivatized and released from the resin to afford the final products. As this synthetic plan developed, variability in the quality of commercial resins (for example, lot to lot variability of loading, and detection of uncapped primary amine sites by a positive Kaiser test on virgin resins) hindered progress. Capricious results in the reductive amination step (variable primary amine performance coupled with cumbersome methods for assessing reaction progress and outcome) were bothersome. The sum of these problems also complicated troubleshooting later steps in the synthesis.

As a means of removing variables in the synthetic scheme, we decided to perform the reductive amination in solution, purify the resulting secondary amine, and couple the resulting construct to the resin.[3] Typically 1 mmol of primary amine was reacted with 0.98 mmol of 4-(4-formyl-3-methoxyphenoxy)butyric acid (**1**) in the presence of 1 mmol *N*,*O*-bis(trimethylsilyl)acetamide and 1.5 mmol of $Na(OAc)_3BH$ in 20 mL of 1,2-dichloroethane (DCE). The reaction mixture was stirred at room temperature for 2 h. Consumption of **1** was monitored by TLC or HPLC. On some occasions, a second aliquot of $Na(OAc)_3BH$ was added to drive the reaction to completion. To the reaction flask was added 10 mL dioxane followed by 1.1 mmol Fmoc-OSu and the reaction mixture stirred over night at room temperature. The reaction product was partitioned between DCM and 1N HCl. The aqueous layer was extracted twice with DCM, the combined organic fractions dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography. This chemistry as described has been run in up to 60 mmol scale with no loss in performance. The carboxylic acid constructs **2** were coupled to aminomethylated polystyrene using diisopropylcarbodiimide (DIC) and 1-hydroxy-7-azabenzotriazole (HOAt), monitoring for complete coupling using the Kaiser test.[4] Fmoc release was accomplished with piperidine/dimethylformamide (DMF) solutions. Resin loadings were determined by Fmoc release analysis. The resins **3** were identical in all respects to resins in which

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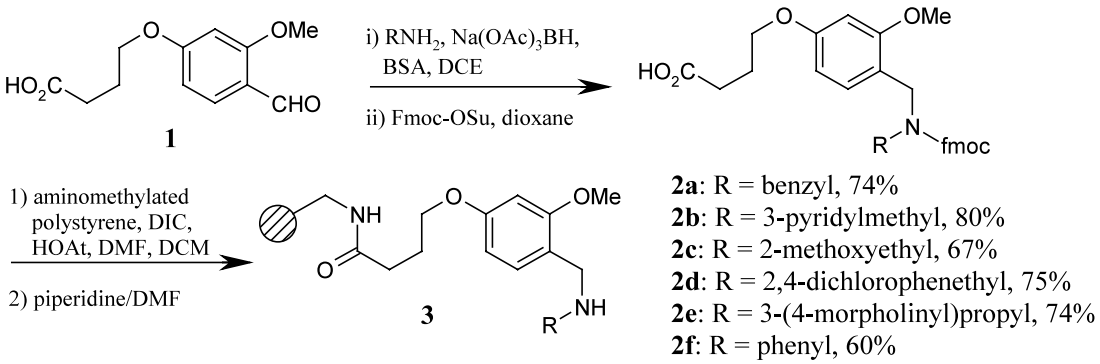

2a: R = benzyl, 74%
2b: R = 3-pyridylmethyl, 80%
2c: R = 2-methoxyethyl, 67%
2d: R = 2,4-dichlorophenethyl, 75%
2e: R = 3-(4-morpholinyl)propyl, 74%
2f: R = phenyl, 60%

the reductive amination on solid-phase had proceeded without complication.

The advantages of synthesizing the constructs **2** and then coupling these to aminomethylated polystyrene are several. The problem of variability among lots of commercially available dialkoxybenzaldehyde resins is eliminated. Amines that are poor partners in the solid-phase reductive amination sequence or are available in limited supply may be employed. Coupling of the constructs **2** to the resin can be easily monitored for completeness. Finally, the procedure is readily scalable.

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