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BAL resin for the preparation of secondary amines☆,☆☆

Pilar Forns,[a,*] Sara Sevilla,[a] Montserrat Erra,[b] Alberto Ortega,[b] Joan-Carles Fernández,[a] Natalia de la Figuera,[a] Dolors Fernández-Forner[b,*] and Fernando Albericio[c,*]

[a]*Almirall & Prodesfarma-Barcelona Science Park Unit, Barcelona Science Park, Josep Samitier 1, 08028 Barcelona, Spain*
[b]*Research Center, Almirall Prodesfarma, Cardener 68-74, E-08024 Barcelona, Spain*
[c]*Barcelona Biomedical Research Institute, Barcelona Science Park, Josep Samitier 1, 08028 Barcelona, Spain*

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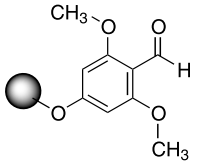
Abstract—Although amino acids anchored through the amino function to BAL resins can not easily be released from the resin by treatment with neat trifluoroacetic acid, we have shown that secondary amines can be obtained from BAL resins using trifluoroacetic acid solutions.

1. Introduction

Solid-phase synthesis strategies are strongly tied to the linker or handle that binds the first building block to the solid support.[2] The bond between the linker and the growing molecule should be stable to conditions and reagents used during the whole synthetic process. However, at the end of the synthesis the linker must allow a smooth release of the target molecule from the support by a treatment that leaves the final molecule unaltered. Considering that the solid-phase synthesis mode was first developed for the preparation of peptides, the vast majority of handles can be considered as protecting groups for the C-terminal carboxylic acid group. Such systems allow only monodirectional growth of the molecule. Several years ago, a novel and more general concept for solid-phase synthesis was developed by one of us. This approach involves attachment of an amine nitrogen, by reductive amination and further acylation, to a tris(alkoxy)benzyl system [Backbone Amide Linker (BAL)][3] and allows bi-directional growth. The BAL strategy has allowed the preparation of hundreds of C-terminal modified peptides, heterocycles, and other small organic molecules, always through amide/peptide bond anchoring.[3,4]



BAL resin

One of our current programs in *Solid-Phase Combinatorial Chemistry* employs the BAL linker for standard amide synthesis and, during the course of this work, we observed several examples in which secondary amines were obtained after the cleavage step.

Very few linkers have been described in the literature that allow the solid-phase preparation of secondary amines,[5,6] and even fewer that allow the anchoring of primary amines for further manipulation to render secondary amines anchored to the support.[7]

Given this background, and although it is known that primary amines (from amino acids) can not easily be released from BAL resin,[8] we decided to initiate a research program aimed at the solid-phase preparation of secondary amines using BAL resin. The approach would involve incorporation of a primary amine onto the solid support, subsequent alkylation of the supported amine, and final acidolytic cleavage.

2. Results and discussion

Two different families of secondary amines were prepared starting from BAL resin, which was obtained by

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* Corresponding authors. E-mail: pforns@pcb.ub.es; dfernand@almirallprodesfarma.com; albericio@pcb.ub.es

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attachment of BAL linker to an aminomethyl polystyrene resin (Fig. 1).

In the first family (Fig. 1A), 1-Alloc-3-amino-pyrrolidine was incorporated onto the BAL resin through reductive amination with $NaBH_3CN$ in DMF/HOAc. Removal of the Alloc group was carried out with Pd(0) using $Me_2NH{\cdot}BH_3$ as an allyl scavenger.[9] Further alkylation of both amines was performed by reductive amination with the corresponding aldehyde and $NaBH(OAc)_3$ in DMF/HOAc. Finally, release of the secondary amines from the resin was carried out with TFA/H_2O (95:5) for 4 h at room temperature. This process gave cleavage yields in the range 60–75% (calculated by weight and taking in account the initial loading of the resin) and good levels of purity (>70%).[10,11]

In the second family (Fig. 1B), incorporation of the primary amine by reductive amination (as described above) was followed by a Petasis multicomponent reaction[12] with glyoxylic acid and boronic acids to give the secondary amine-supported resin.[10] In this case, a study of the cleavage conditions to render *N*-alkyl-amino acids was carried out and the results are shown in Table 1.

Although the best results were obtained using TFA/DCM at 60°C for 1 h (nearly quantitative yield), se-

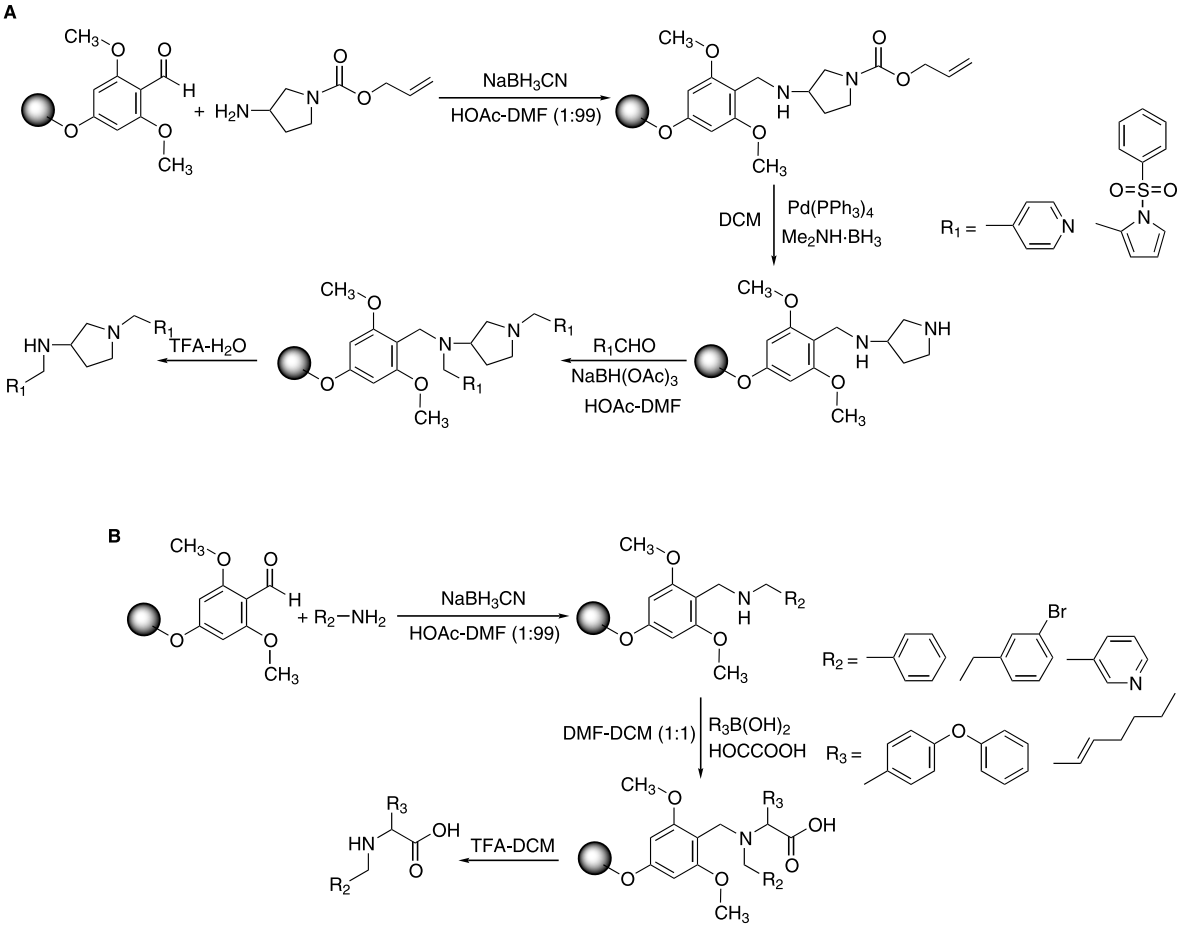

Figure 1. Synthetic schemes involved in the preparation of secondary amine compounds.

Table 1. TFA cleavage conditions, yields[a] and purities[b]

	TFA/DCM (50:50)			TFA/DCM (95:5)		
	2 h, 25°C	16 h, 25°C	1 h, 60°C	2 h, 25°C	16 h, 25°C	1 h, 60°C
Yield (%)	20–85[c]	75–90	85–100	15–70[c]	70–100	85–100
Purity (%)	65–95	89–98	90–95	60–98	90–98	85–98

[a] Yields were calculated by weight, taking as a reference the amount obtained when the resin was treated with TFA/DCM (95:5) for 6 h at 60°C, and agree with those expected based on the initial loading of the resin.

[b] As determined at $\lambda = 210$ nm.

[c] When the cleavage was carried out for 2 h at 25°C, slightly better results were obtained with TFA/DCM 50:50 compared to 95:5. This can be interpreted as being due to better swelling of the resin with a higher proportion of DCM.[13]

condary amines can also be released at low temperature with longer cleavage times. For example, when the procedure was carried out for 16 h at 25°C, very similar results were obtained. As the purity of both cleavage products was similar (see Table 1), the conditions at 60°C are recommended on the basis of the shorter cleavage times. Furthermore, only slight differences were found between TFA/DCM in proportions 50:50 and 95:5, and so the milder conditions are preferred.

3. Conclusions

In conclusion, the release with TFA of secondary amines from BAL resin opens new possibilities for the preparation of this kind of compound by the solid-phase mode in combinatorial programs.

4. Experimental protocols

4.1. General procedure for anchoring the amine onto the resin by a reductive amination reaction

The amine (5 equiv.) and $NaBH_3CN$ (5 equiv.) in AcOH/DMF (1:99) (8 mL/g of resin) were added to the BAL-resin (1 mmol/g) (preswollen in DMF) and the mixture was stirred overnight at 60°C. The resin was filtered off and washed with DMF, AcOH/DMF (1:99), DMF, DIEA/DMF (1:19), DMF, DCM, and dried.

4.2. Removal of the Alloc group

$Me_2NH{\cdot}BH_3$ (40 equiv.) in dry DCM (20 mL/g of resin) was added to the resin-bound amine, followed by $Pd(PPh_3)_4$ (0.1 equiv.). Argon was bubbled through the mixture, which was stirred at room temperature for 1 h. The resin was filtered off, washed with DCM, and the removal process was repeated. The resin was washed with DCM, 0.2% TFA in DCM, DCM, DIEA/DMF (1:19), dioxane/H_2O (9:1), MeOH, DMF, DCM, and dried.

4.3. Alkylation of amine by reductive amination reaction

A solution of the aldehyde (20 equiv.) in DMF (16 mL/g of resin) was added to the resin-bound amine, the AcOH (0.4% with respect to the DMF) was added and the mixture was stirred at room temperature for 1 h. $NaBH(OAc)_3$ (20 equiv.) was added and the reaction stirred overnight at room temperature. The resin was filtered off and washed as described above. The same protocol was applied to ketones as well as aldehydes.

4.4. Petasis multicomponent reaction

Solutions of glyoxylic acid (4 equiv.) in DCM/DMF (95:5) (8 mL/g of resin) and boronic acid (4 equiv.) in DMF (4 mL/g of resin) were added to the resin-bound amine. The mixture was stirred for 62 h at room temperature. The resin was filtered off and then washed with DCM, DMF, MeOH, DCM, and dried.

4.5. Cleavage

The resin was treated with TFA solution (20 mL/g of resin) either at 25 or at 60°C for the appropriate cleavage time. The resin was filtered off, washed with TFA solution, and the combined filtrates were evaporated to dryness, redissolved in MeOH and evaporated again to afford the target product.

Acknowledgements

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1. Abbreviations used for amino acids and the designations of peptides follow the rules of the IUPAC-IUB Commission of Biochemical Nomenclature in *J. Biol. Chem.* **1972**, *247*, 977–983. The following additional abbreviations are used: AcOH, acetic acid; Alloc, allyloxycarbonyl; BAL, backbone amide linker; Barlos resin, 2-chlorotrityl chloride-resin; DCM, dichloromethane; DIEA, *N*,*N*-diisopropylethylamine; DMF, *N*,*N*-dimethylformamide; MeOH, methanol; TFA, trifluoroacetic acid.
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