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Efficient loading of primary alcohols onto a solid phase using a trityl bromide linker

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ABSTRACT

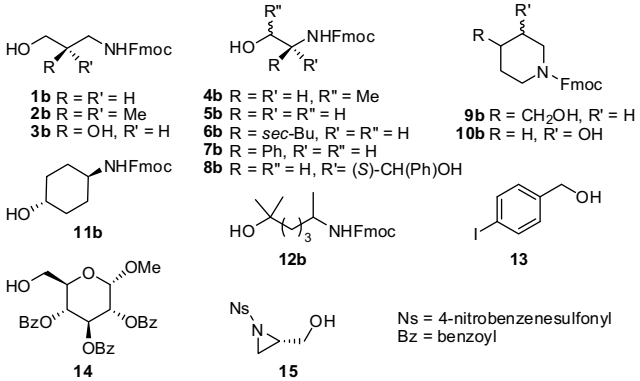
The Letter describes an improved, rapid and mild strategy for the loading of primary alcohols onto a polystyrene trityl resin via a highly reactive trityl bromide linker. This protocol facilitates an efficient resin loading even of acid-sensitive or heat-labile alcohols, which otherwise require expensive or non-commercial resin types. Secondary alcohols were only attached in moderate to low yields, while attempts to load a tertiary alcohol expectedly failed. Importantly, selective attachment of diols via a primary alcohol group in the presence of more hindered alcohol groups proved possible. The effects of activation time and reagent excess as well as alcohol structure were investigated. This improved method provides a convenient access to O-linked resin-bound *N*-Fmoc-protected amino alcohols that may be employed in SPS of peptides with C-terminal alcohol functionalities. In the case of a sensitive alcohol containing an activated aziridine functionality, the use of the trityl bromide linker proved superior to a recently described silver triflate-assisted trityl chloride resin-based procedure.

Organic synthesis carried out on solid supports is a key technology for rapid and efficient production of compound libraries that requires a careful choice of resin type and selection of an adequate linker for anchoring the starting material.[1] Recently, we have reported on improved methods for solid-phase synthesis (SPS) of secondary and tertiary amines[2] including philanthotoxin analogs,[3,4] amino acid derivatives,[5] heterocyclic scaffolds,[6] and biologically active α-peptide/β-peptoid oligomers.[7]

In the present work, we extend our studies on SPS methodology to the development of a rapid and mild means for the loading of alcohols onto a solid support with the purpose to circumvent limitations of existing methods. Thus, in order to provide a high degree of versatility, such a protocol should facilitate efficient loading of alcohols containing acid-sensitive or heat-labile moieties. While a number of strategies[8] using dihydropyran- or silyl-based[9,10] as well as trityl linkers[11] have previously been described for this purpose, these methods have limitations mainly due to prolonged reaction times and harsh conditions and reagents, such as high temperatures or strong bases. Recently, Lundquist et al. published a procedure employing silver triflate-assisted attachment of alcohols to a trityl chloride resin,[12] a procedure that evades the limited reactivity of the standard trityl chloride linker, but suffers from potential problems due to formation of insoluble silver chloride precipitate on the resin as well as partial degradation of acid-sensitive alcohols. We now provide an alternative employing a considerably more reactive trityl bromide linker, easily generated in situ from a trityl alcohol resin.

In solution-phase chemistry it is well established that trityl bromide (TrtBr) is the reagent of choice when a high reactivity is needed for difficult O-protections.[13] By contrast, TrtBr resins have been surprisingly poorly investigated, and an exhaustive survey of the literature revealed only applications for loading of carboxylic acids[14] and phenols.[15]

Thus, we set out to investigate the loading of primary amino alcohols (Scheme 1) onto a polystyrene TrtBr resin (PS-TrtBr) prepared from a trityl alcohol resin (PS-TrtOH). In addition, experiments with secondary and tertiary alcohols were undertaken.



Scheme 1. The array of alcohols examined in this study (**1b–12b** were prepared from the corresponding unprotected amino alcohols **1a–12a**).

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Fmoc-protected amino alcohols were employed due to their general synthetic utility, ease of preparation, and convenient HPLC analysis with diode-array detection (HPLC–DAD) of the reaction mixtures. The versatility of the strategy was exemplified by subsequent conversion of the products into an amino acid derivative containing a C-terminal alcohol as well as a chiral *N*-(ω-hydroxyalkyl)-functionalized β-aminosulfonamide.

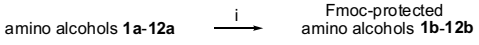
First, amino alcohols **1a**–**12a** were N-protected by a standard procedure described by Calveras et al. (Scheme 2).[16] Thus, building blocks **1b**–**12b** were obtained in excellent yields by using Fmoc–OSu and a low excess of the corresponding amino alcohols in dioxane–water at room temperature (Table 1).[17]

In order to establish conditions that enable an efficient loading of alcohols in general, the initial focus was on optimizing the loading of primary alcohol **1b**[16] onto a commercially available PS-TrtOH resin (loading: 1.64 mmol/g) via an intermediate PS-TrtBr resin. This was considered a suitable test reaction that should preferably be achievable at room temperature (Scheme 3).

Several reaction parameters were varied, including the excess of acetyl bromide (AcBr) and alcohol **1b** as well as the activation and loading time (Table 2). Initially, the conversion to PS-TrtBr resin was performed by using 30 equiv of AcBr for 90 min in dry dichloromethane (DCM), examining the influence of the amount of **1b** and the loading time (Table 2, entries 1–3). Treatment with 2 equiv of the alcohol for 10 min with addition of 5 equiv of *i*-Pr_2EtN as base gave a satisfactory result. The effect of solvent was examined by exchanging DCM for *N*-methyl-2-pyrrolidone (NMP),[12] but this resulted in a significantly decreased yield (Table 2, entry 4).

Next, by decreasing the amount of AcBr and varying the activation time, it was found that 10 equiv and 30 min, respectively, afforded a high yield (Table 2, entry 7), whereas a smaller amount of AcBr (Table 2, entry 8) led to a somewhat decreased yield. Thus, the conditions selected for subsequent studies involving an array of different alcohols comprised activation with 10 equiv of AcBr for 30 min, followed by loading of 2 equiv of the alcohol in the presence of 5 equiv of *i*-Pr_2EtN for 10 min in dry DCM under nitrogen.[18]

Hence, these optimal conditions were employed for the loading of several primary alcohols.[19] After the standard cleavage procedure employing 2% TFA–DCM,[20,21] yields were excellent to good even for more sterically hindered primary amino alcohols **2b** and **6b**, while **7b** only afforded a moderate yield. In addition, alcohol

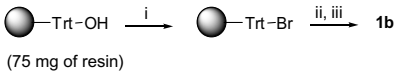


Scheme 2. Reagents and conditions: (i) amino alcohol **1a**–**12a** (1.2 equiv), Fmoc-OSu (1.0 equiv), 1,4-dioxane–water (4:1), rt, 16 h, 37–99%.

Table 1
Synthesis of Fmoc-protected amino alcohols **1b**–**12b**

Product	**1b**	**2b**	**3b**	**4b**	**5b**	**6b**
Yield (%)	97	97	91	93[a]	97	97
Product	**7b**	**8b**	**9b**	**10b**	**11b**	**12b**
Yield (%)	99	99	96	96	37[b]	94

[a] 2.2 equiv of **4a** was used.
[b] Amino alcohol hydrochloride was used; 1.2 equiv of Et_3N was added prior to the addition of Fmoc–OSu.



Scheme 3. Reagents and conditions: (i) AcBr, dry DCM, rt, N_2; (ii) **1b**, *i*-Pr_2EtN, dry DCM, rt, N_2; (iii) washing procedure then cleavage with 2% TFA–DCM.

Table 2
Loading of primary alcohol **1b** onto a prepared PS-TrtBr resin

Entry	AcBr (equiv)	Activation (min)	**1b** (equiv)	Loading (min)	Yield (%)[a]
1	30	90	5	5	73
2	30	90	5	30	65
3	30	90	2	10	74
4	30	90	2	10	38[b]
5	30	90	2	10	66[c]
6	10	10	2	10	44
7	**10**	**30**	**2**	**10**	**90**
8	5	30	2	10	79

[a] Determined by analytical HPLC–DAD (254 nm) by comparison with a reference chromatogram of the pure starting material.
[b] Dry NMP was used in the loading step.
[c] 1 g of PS-TrtOH resin was used.

5b with a short aliphatic chain, piperidine derivative **9b**, benzyl alcohol **13**, and partially protected methyl glucopyranoside **14** were included. Except for carbohydrate derivative **14**, all yields were only a little lower than that found for compound **1b** (Table 3).

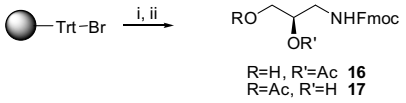
In addition, the attachment of (*N*-nosylaziridin-2-yl)methanol (**15**) onto a trityl resin was examined as an example of a procedure employing a highly sensitive alcohol. As the standard cleavage procedure led to a complex mixture, aziridine ring-opening[6] was subsequently performed by using 10 equiv of 3-phenylpropylamine in THF at room temperature overnight, to provide a β-amino-β′-hydroxysulfonamide in 87% overall yield. In this case, the procedure of Lundquist et al.[12] gave a significantly lower overall yield (35%), demonstrating the mildness and efficiency of the present PS-TrtBr methodology. Subsequently, we examined the potential of the method for the loading of secondary alcohols **4b**, **10b**, and **11b**, but as expected only quite low yields were obtained in all cases. Attempts to improve the loading of **4b** included use of dry 1,2-dichloroethane (DCE) as solvent at elevated temperature. However, even increasing the amount of **4b** to 4 equiv and extending the reaction time still resulted in a low loading yield (13–25%). The use of microwave (MW) irradiation conditions appeared to be less efficient than conventional heating (Table 3). Likewise, attempts to use a tertiary alcohol (**12b**) failed to provide useful results. Thus, this methodology should allow selective loading of primary alcohols in the presence of secondary or tertiary alcohol functionalities.

Accordingly, the loading of diols **3b** and **8b** onto PS-TrtBr resulted in yields comparable to those obtained for sterically hindered primary alcohols already examined. Moreover, to confirm the practical utility of the protocol, compounds **1b**, **3b**, and **8b** (obtained after successive loading and cleavage from 125 mg of starting resin) were reisolated in 70%, 53%, and 55% yields, respectively, after preparative HPLC–DAD (97–100% purity at 267 nm). To determine the selectivity between primary and secondary hydroxy groups in diol **3b**, acetylation of the resin with Ac_2O–*i*-Pr_2EtN–

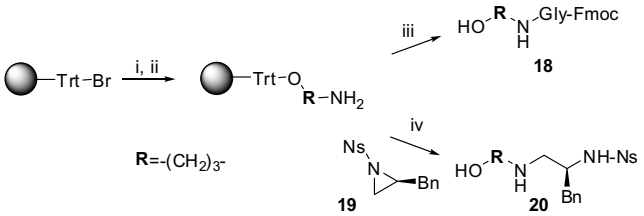
Table 3
Loading of more hindered primary, secondary, and tertiary alcohols as well as diols[a]

Product	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**
Yield (%)	89	67	24[b]	85	74	55	58
Product	**9b**	**10b**	**11b**	**12b**	**13**	**14**	**15**
Yield (%)	66	25	17[c]	<1[d]	71	20	87[e]

[a] Using the optimized conditions described above.
[b] Using 4 equiv of **4b** at rt for 1 h, 2 equiv of **4b** at 50 °C for 1 h in DCE, or 4 equiv of **4b** at 60 °C for 1 h in DCE under MW irradiation conditions gave yields of 25%, 13%, and 21%, respectively.
[c] Addition of amino alcohol was performed in DCM–DMF (4:1).
[d] Obtained with 4 equiv of **12b** at rt for 1 h.
[e] Determination of the loading of **15** required a subsequent ring-opening using 3-phenylpropylamine as **15** is unstable under the cleavage conditions.



Scheme 4. Reagents and conditions: (i) **3b** (2 equiv), *i*-Pr_2EtN (5 equiv), dry DCM, rt, 10 min, N_2; (ii) Ac_2O–DIPEA–DMF (1:2:3), 60 °C, 4 h, washing procedure, then cleavage with 2% TFA–DCM.



Scheme 5. Reagents and conditions: (i) **1b** (2 equiv), *i*-Pr_2EtN (5 equiv), dry DCM, rt, 10 min, N_2; (ii) 20% piperidine–DMF, rt, 2 × 30 min; (iii) Fmoc-Gly-OH (3 equiv), TBTU (3 equiv), *i*-Pr_2EtN (6 equiv), dry DMF, rt, 1 h, washing procedure then cleavage with 2% TFA–DCM, 92% overall yield; (iv) **19** (2 equiv), MW, 80 °C, 15 min, washing procedure then cleavage with 2% TFA–DCM, 74% overall yield.

DMF (1:2:3) at 60 °C for 4 h prior to cleavage provided acylated compound **16**. Its purity and identity were confirmed by analytical HPLC–DAD and by ^{1}H NMR analysis (a characteristic downfield shift of C*H*OAc was observed), respectively. Since compound **17** was not detected, a very high selectivity for the primary hydroxy group was proved (Scheme 4).

Two examples of SPS applications of the developed PS-TrtBr protocol are depicted in Scheme 5. With freshly prepared PS-TrtBr as a starting point, an N-alkylated amino acid derivative containing a C-terminal alcohol **18** was prepared in 92% overall yield by using standard SPS procedures.[22] Moreover, compound **20** was prepared in high purity and good yield by performing a MW-assisted ring-opening procedure, as recently described by Crestey et al.,[5] with (*S*)-*N*-(*p*-nitrobenzenesulfonyl)-2-benzylaziridine **19**.[23] These results demonstrate that construction of peptides as well as amino-sulfonamides is feasible. Likewise, SPPS starting from diol **3b** enables preparation of N-terminal peptide aldehydes via a post-cleavage oxidation.[24]

In conclusion, a novel, mild, highly selective, and rapid (<2 h) method for preparation of resin-bound primary alcohols in good yields has been developed. The protocol offers the advantage of avoiding otherwise long loading times by using a cheap commercial starting resin, which only requires a simple activation prior to the loading step. Notably, similarly mild alcohol attachments (e.g., via silyl-based linkers) require expensive or non-commercial resin types, which in addition are cleaved under less mild conditions and in some instances require special equipment.[10a,c] Further studies concerning construction of new scaffolds from the O-linked resin-bound intermediates are in progress.

Acknowledgments

We thank the Lundbeck Foundation for financial support to F.C. and the *Brødrene Hartmanns Fond* (Copenhagen) for a grant.

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17. *Typical procedure for Fmoc protection of amino alcohols*: To a solution of 3-amino-2,2-dimethyl-1-propanol (**2a**; 1.1 g, 10.7 mmol, 1.2 equiv) in a mixture of dioxane–water (20 mL) was added Fmoc-OSu (3.0 g, 6.7 mmol) over 5 min. The reaction mixture was stirred for 16 h at room temperature and concentrated in vacuo. Workup as previously described by Calveras et al.[16] gave 9*H*-fluoren-9-ylmethyl (3-hydroxy-2,2-dimethylpropyl)carbamate (**2b**) as a white powder (2.8 g, 97%). Mp 118–121 °C. TLC R_f = 0.5 (heptane–EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (d, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 5.12 (br s, 1H), 4.45 (d, *J* = 6.6 Hz, 2H), 4.21 (t, *J* = 6.6 Hz, 1H), 3.22 (br s, 1H), 3.18 (s, 2H), 3.03 (d, *J* = 5.5 Hz, 2H), 0.83 (s, 6H). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.91; H, 6.98; N, 4.33.
18. *Typical procedure for successive activation of trityl alcohol resin and alcohol attachment*: AcBr (91 μL, 1.23 mmol, 10 equiv) was added to PS-TrtOH resin (1.64 mmol/g, 75 mg, 0.12 mmol) swollen in dry DCM (2 mL) under N_2 at room temperature. The mixture was agitated for 30 min, then drained and washed with dry DCM (3 × 2 mL for 5 min). A solution of the desired alcohol (0.25 mmol, 2 equiv) and *i*-Pr_2EtN (107 μL, 0.62 mmol, 5 equiv) in dry DCM (2.5 mL) was added and the reaction mixture was stirred for 10 min under N_2. The resin was drained, washed with DMF, dioxane, MeOH, and DCM (each 3 × 5 mL for 5 min), and then cleaved with 2% TFA–DCM (2 × 2 mL for 30 min). The resin was further eluted with DCM (2 mL), and the resulting solutions were combined and co-evaporated with toluene in vacuo. The crude material was purified by preparative reversed-phase HPLC–DAD using a 21.2 × 250 mm Phenomenex C18 column (5 μm, 100 Å) in a system consisting of two preparative-scale pumps, an autosampler and a multiple-wavelength UV detector.
19. Elementary analyses for novel Fmoc-protected amino alcohols were obtained with satisfactory results: compound **3b**: Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 69.04; H, 6.05; N, 4.47; compound **9b**: Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.65; H, 6.83; N, 4.19. compound **10b**: Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.68; H, 6.79; N, 4.61.
20. A minor peak, assumed to be the trifluoroacetate of the alcohol formed during the TFA treatment, was usually observed in HPLC–DAD analysis of the reaction mixtures after our standard cleavage procedure with 2% TFA–DCM. An alternative cleavage procedure,[21] employing successive additions of DCM (1.5 mL), 0.5 M HCl in DCM (1.0 mL), water (25 μL), and triisopropylsilane (TIS, 25 μL), followed by shaking for 1 h, was tested with a resin loaded with alcohol **1b**. In this case, formation of the by-product was avoided; a 95% yield of the desired compound was observed.
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23. *Typical procedure for MW-assisted ring-opening*: To a resin loaded with alcohol **1b**, prepared according to the above procedure using PS-TrtOH (100 mg, 0.16 mmol), was added 20% piperidine–DMF (3 mL). The resin was stirred for 0.5 h and then drained. This was repeated once, followed by washings with DMF, MeOH, and CH_2Cl_2 (each 3 × 2 mL for 5 min), and lyophilization overnight. After addition of aziridine **19** (104 mg, 0.33 mmol, 2 equiv) in DCE (2 mL), the resin was heated to 80 °C under MW irradiation for 15 min. The

resin was drained, washed with DMF, MeOH, and CH_2Cl_2 (each 3 × 2 mL for 5 min), and then the product was cleaved with TFA–DCM (2:98) (2 × 2 mL for 0.5 h). The resin was further eluted with DCM (2 mL) and the resulting solutions were combined and co-evaporated with toluene in vacuo. The crude material was purified by preparative reversed-phase HPLC to give the trifluoroacetic acid salt of *N*-{(1*S*)-1-benzyl-2-[(3-hydroxypropyl)amino]-ethyl}-4-nitrobenzenesulfonamide **20** as a colorless oil (61 mg, 74% overall yield). ^{1}H NMR (300 MHz, CD_3OD) δ: 8.10 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 6.87–7.02 (m, 5H), 3.72–3.83 (m, 3H), 3.08–3.36 (m, 4H, partially under the solvent peak), 2.77 (dd, J = 14.0 Hz and J = 4.7 Hz, 1H), 2.46 (dd, J = 14.0 Hz and J = 9.9 Hz, 1H), 1.96 (q, J = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ: 150.2, 145.4, 135.3, 129.2 (2C), 129.1 (2C), 128.2 (2C), 127.5, 124.7 (2C), 62.2, 53.7, 52.2, 49.5, 39.1, 27.5. RP-HPLC (267 nm): >99.9% purity. HRMS (*m*/*z*): $[M+H]^+$ calcd for $[C_{18}H_{24}N_3O_5S]^+$ 394.1437; found 394.1421; ΔM 4 ppm.

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