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Expedient Protocol for Solid-Phase Synthesis of Secondary and Tertiary Amines

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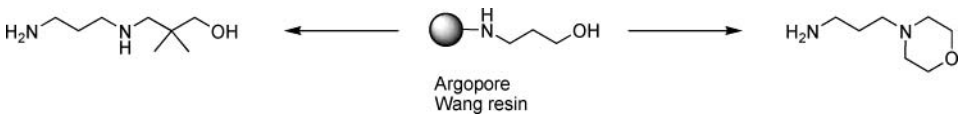
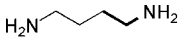
ABSTRACT

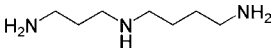


An expedient solid-phase synthetic approach to secondary and tertiary amines was developed. The protocol employs conversion of resin-bound amino alcohols to the corresponding iodides, followed by iodide displacement with primary or secondary amines or with unprotected amino alcohols. This two-step procedure, affording products in good to excellent yields, is suitable for solid-phase synthesis of polyamines.

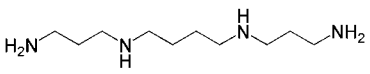
Di- and polyamines such as putrescine (**1**), spermidine (**2**), and spermine (**3**) are ubiquitous in eukariotic cells.[1] Simple *N*-alkylated analogues of **3** have been investigated as potential chemotherapeutic leads.[2] Furthermore, polyamine derivatives, including wasp and spider toxins, have been shown to interact with ion channels in the central and peripheral nervous systems.[3] Therefore, synthetic analogues of these toxins are of considerable interest as potential therapeutic lead compounds[4] and as probes for receptor specificity studies.[5]



1 putrescine



2 spermidine



3 spermine

To obtain chemically diverse libraries of polyamine toxins for structure−activity relationship (SAR) studies on ionotropic glutamate receptors and nicotinic acetylcholine receptors,[3] several methods for their solid-phase organic synthesis (SPOS) have been investigated. Introduction of secondary and tertiary amino functionalities is obviously a crucial step in the construction of polyamines on solid phase,[6] but also in the SPOS of small molecule libraries.[7]

Previously, construction of polyamine chains on solid phase has been achieved by reduction of resin-bound imines[8]

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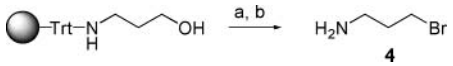
or polyamides.[9] Recently, Fukuyama−Mitsunobu *N*-alkylation has emerged as a versatile method for sequential SPOS of polyamines,[10] and also the formation of tertiary amines mediated by (cyanomethyl)trialkylphosphonium iodide has been reported.[11] Furthermore, alkylation of resin-bound sulfonamides with alkyl bromides,[12] as well as S_N2 reactions employing amines together with halides,[13] methanesulfonates,[14] *p*-toluenesulfonates,[15] or nitrobenzenesulfonates[16] have been described.

Preliminary alkylation experiments with resin-bound methanesulfonate, 2- and 4-nitrobenzenesulfonates, or imidazolylsulfonate[17] led to low yields and purities in our hands. This was possibly due to a competing transsulfonation, as previously observed in *N*-alkylation of resin-bound piperazine with 2-nitrobenzenesulfonates.[16b]

Accordingly, further exploration of the halogen displacement strategy seemed an attractive alternative. The present paper describes the development of a new, efficient, and versatile protocol consisting of conversion of resin-bound aliphatic alcohols into iodides and subsequent displacement by primary or secondary amines as well as unprotected amino alcohols.

Initially, various reagents for the on-resin conversion of *N*-trityl-linked 3-amino-1-propanol to the corresponding bromide were investigated. The selected reagent combinations were CBr_4-PPh_3,[18] Br_2-PPh_3,[19] and NBS−PPh_3,[20] as well as the corresponding reagent pairs containing PBu_3. The performance of these reagents was judged from the purity of the isolated 3-bromo-1-propaneamine (Table 1). Bromine was superior to the other reagents and led to the desired product, **4**, in high yield. By contrast, the use of carbon tetrabromide or NBS resulted in recovery of large amounts of 3-amino-1-propanol along with the formation of **4**. In the case of NBS−PBu_3 the formation of ∼10% of *N*-(3-aminopropyl)succinimide was observed. The reagent pairs Br_2-PPh_3 and Br_2-PBu_3 performed equally well. Thus, PPh_3 was chosen for subsequent investigations due to its higher stability toward air.

Table 1. Test of Reagents for the Preparation of Resin-Bound Bromides[a]



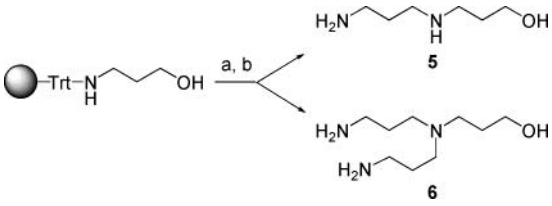
4

entry	phosphine	reagent	purity of **4**,[b] %
1	PBu_3	Br_2	>95
2	PPh_3	Br_2	>95
3	PBu_3	CBr_4	∼75
4	PPh_3	CBr_4	∼5
5	PBu_3	NBS	∼35
6	PPh_3	NBS	∼55

[a] Reagents and conditions: (a) Br_2, CBr_4 or NBS (3 equiv), PBu_3 or PPh_3 (3 equiv), CH_2Cl_2, N_2, 16 h; (b) TFA/$CDCl_3$ (1:1), 1 h. [b] Estimated from ^1H NMR spectra ($CDCl_3$/TFA 4:1).

Treatment of the resin-bound 3-bromo-1-propaneamine with 3-amino-1-propanol resulted in pronounced cross-linking, as shown by the concomitant isolation of **6** after cleavage with TFA (Table 2). It was assumed that the use of a resin with a lower loading would result in diminished cross-linking, due to the statistically larger distance between

Table 2. Alkylation of Trityl Resins with Different Degrees of Loading[a]



entry	resin loading, mmol/g	solvent	ratio **6**:**5**[b]
1	1.28	DMF	0.19
2	1.28	NMP	0.29
3	0.52	DMF	0.05
4	0.52	NMP	0.27
5	0.52	THF/PhMe	N.D.[c]

[a] Reagents and conditions: (a) Br_2 (5 equiv), PPh_3 (5 equiv), CH_2Cl_2, N_2, 16 h; (b) 3-aminopropanol (1.0 M), DMF, NMP or THF/PhMe (1:1), 50 °C, 6 h. [b] Estimated from ^1H NMR. [c] Not determined due to low conversion.

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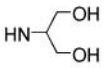
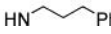
adjacent alkyl bromides on the solid support. To test this hypothesis, a resin with ~40% (0.52 mmol/g)[21] of the original loading was prepared. This was achieved by performing a partial loading of *O*-trimethylsilyl (TMS) protected 3-amino-1-propanol (0.5 equiv) onto the polystyrene trityl chloride resin. The residual chlorine functionalities were end-capped by treatment with 10% diisopropylethylamine (DIPEA) in methanol, and finally the TMS group was removed with tetrabutylammonium fluoride (TBAF). After bromination of this trityl resin with Br_2-PPh_3, and subsequent alkylation with 3-amino-1-propanol in selected solvents, the product was cleaved from the resin with TFA. Only 5% of the tertiary amine **6** was obtained when the alkylation step was performed in DMF, whereas the alkylation in *N*-methylpyrrolidinone (NMP) resulted in 27% of **6** (Table 2).

The degree of cross-linking (5% in DMF) was found acceptable, and additional experiments were performed on this trityl resin (0.52 mmol/g). Displacement of a bromide, and also an iodide prepared under previously described conditions (I_2-PPh_3 and imidazole),[22] resulted in impure crude products, and only 20−30% yields (Table 3) were obtained after reversed-phase vacuum liquid chromatography (VLC). Since neither the bromides nor the iodides performed satisfactorily on the trityl resins, a macroporous Argopore Wang resin in combination with a carbamate linker was considered. When performing the iodide displacement sequence with this resin, close to quantitative conversions were observed.[23]

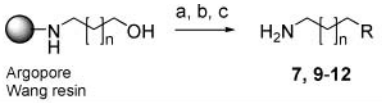
Table 3. Solid-Phase Synthesis of Amines by Displacement of Halides on a Polystyrene Trityl Resin[a]

compd	R-group	yield (%)[d]
7[b]		28 %
8[b]		20 %
9[c]		30 %

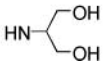
[a] All compounds were synthesized by using general procedure A.[23] [b] Iodide displacement. [c] Bromine displacement. [d] Yield of the corresponding bis(TFA) salts after reversed-phase VLC.

To test the scope of this SPOS protocol, portions of *p*-nitrophenylcarbonate-activated Argopore Wang resin were loaded with 3-amino-1-propanol, 6-amino-1-hexanol, phenylalaninol, or 4-hydroxymethylpiperidine, and the hydroxy groups were converted into iodides. Subsequently, the iodides were displaced with different types of amines, and post-cleavage examination of the products showed that the method is efficient for the preparation of secondary as well as tertiary amines in high purities (**7** and **9**−**12**, Table 4). Noticeably, unprotected amino alcohols were employed without any detectable ether formation. Compounds **11** and **12** were prepared in somewhat lower yield but still with a high purity.

Table 4. Solid-Phase Synthesis of Amines by Displacement of Iodides on Argopore Wang Resin[a]



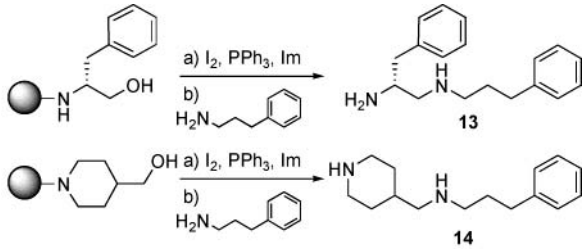
Argopore Wang resin — **7, 9-12**

compd	n	R-group	yield (%)[b]/ purity (%)[c]
7	1		88/> 95
9	1		78/> 95
10	1		86/> 95
11	4		63/> 95
12	4		51/> 90

[a] Compounds **7** and **9**−**12** were synthesized by using general procedure B.[23] Reagents and conditions: (a) I_2 (5 equiv), PPh_3 (5 equiv), imidazole (5 equiv), CH_2Cl_2, N_2, 16 h; (b) amine (1.0 M, 10 equiv), DMF, 50 °C, 6 h; (c) TFA/CH_2Cl_2 (1:1), 1 h. [b] Yields are based on the weight of crude material relative to the initial loading. [c] Estimated from ^{1}H NMR.

The products **13** and **14** were prepared on larger scale, as purification by reversed-phase VLC was necessary. The isolated yields were 55% and 43%, respectively, which showed that acceptable yields could be obtained in alkylations of relatively hindered alcohols by using this protocol (Scheme 1).

Scheme 1. Synthesis of **13** and **14** on Argopore Resin



In summary, an expedient SPOS protocol for the preparation of amines has been developed. The scope of this strategy was shown to include formation of secondary and tertiary amines in good yields and high purities. Also, the use of protecting groups could be omitted when employing amino alcohols as the nucleophile. We envisage that this synthetic

(21) The loading was calculated from ^{1}H NMR spectra of cleaved amino alcohol with DMSO added as internal quantitative standard.

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(23) Consult the Supporting Information for details.

scheme may be exceedingly useful for the introduction of amino functionalities in SPOS of compound libraries, as it is a both cheap and efficient method for conversion of hydroxy groups into amino functionalities. In this protocol the Argopore Wang resin proved superior to the polystyrene trityl resin. Whether this difference observed between the two types of resin is due to the polymer properties and/or the linker remains to be investigated in detail.

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds **7** and **9**−**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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