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LETTERS

Versatile solid-phase synthesis of secondary amines from alcohols. Development of an *N*-Boc-(*o*-nitrobenzene)sulfonamide linker

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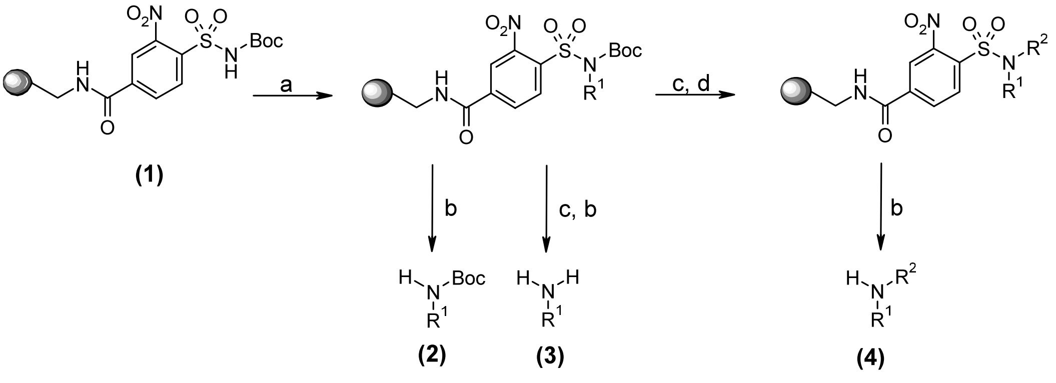
Abstract—The development of a versatile amine releasing linker based on the modified *o*-nitrobenzene sulfonamide protective group is described. This new *N*-Boc-*o*-nitrobenzenesulfonamide (Boc-ONBS) linker enables the elaboration on resin of primary and secondary amines by sequential substitution of the sulfonamide moiety using the Mitsunobu reaction. A 16-member array of secondary and Boc protected primary amines was then prepared using this linker. © 2003 Elsevier Science Ltd. All rights reserved.

Amine releasing linkers[1] possess the combined advantage of acting as an anchor point to the solid support as well as in some cases providing temporary protection for an otherwise reactive functionality.[2] Generally such systems do not allow modification of the amine groups whilst immobilised on resin to give more complex amines. We recently reported a linker[3] based on Fukuyama's *o*-nitrobenzenesulfonyl protecting group,[4] which releases primary or secondary amines in good yields and purity. However, one limitation of this linker system is that it requires functionalisation of one of the amine substituents in solution prior to immobilisation on the solid support.

Herein we wish to report a modified linker that remedies this shortcoming. This Boc-ONBS linker (**1**) enables on-bead preparation of both primary (free or Boc-protected) and secondary amines from alcohol precursors via the Mitsunobu reaction.



Scheme 1. *Reagents and conditions*: (a) R^{1}OH, Ph$_3$P, DEAD, THF, rt; (b) DBU, mercaptoethanol, MeCN, rt; (c) TFA, CH$_2$Cl$_2$, rt; (d) R^{2}OH, Ph$_3$P, DEAD, THF, rt.

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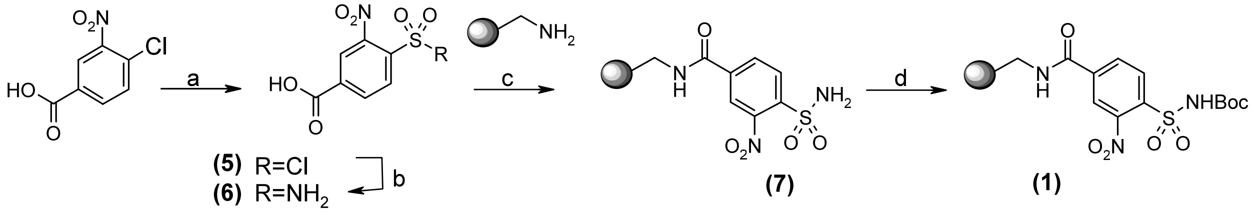
As recently shown by Fukuyama[5] the presence of the Boc protective group ensures that only mono alkylation occurs under Mitsunobu conditions,[6,7] and allows synthesis of either Boc (**2**) or unprotected amines (**3**) on cleavage with a thiol (Scheme 2). Secondary amines (**4**) are accessible firstly by removal of the Boc group and then by performing a second Mitsunobu reaction. The Boc-ONBS linker (**1**) was prepared from readily available starting materials as shown in Scheme 2. The 4-chloro-3-nitrobenzoic acid precursor was converted to the sulfonyl chloride (**5**), which was then treated with ammonia to give primary sulfonamide (**6**). Attachment of (**6**) to aminomethyl polystyrene resin (1 mmol/g) gave primary sulfonamide resin (**7**) and Boc protection gave the required immobilised linker (**1**) in good overall yield.

The feasibility of using linker (**1**) to produce amines was firstly tested using an analytical construct[8] (Fig. 1). Introduction upstream of the chemically orthogonal Dde linker[9] (Linker 1) enabled 'analytical cleavage' of small resin samples[10] to release amine-tagged fragments, analysis of which indicated the progress of each reaction step. These cleaved derivatives (**10a–c**) contained a secondary amine to ensure reliable ionisation in ESI positive mode mass spectrometry (a MS sensitiser) and were present as an equimolar isotopic mixture to produce a diagnostic doublet in the spectrum (MS peak splitter). Coupling of the sulfonamide linker (**6**) to the amine resin (**8**)[10] and Boc protection afforded analytical construct (**9**). This was subsequently derivatised with *o*-methoxybenzyl alcohol and 1-naphthyl alcohol, in the manner described in Scheme 1, enabling synthesis of a previously characterised secondary amine (**11**). After each step of the reaction sequence, analytical cleavage and MS analysis confirmed a successful transformation, with a final conventional cleavage at the *o*-NBS linker affording the amine (**11**) in good yield and purity.

The utility of the linker was exemplified in the preparation of an array of Boc protected primary amines and secondary amines (Table 1). Following the first Mitsunobu reaction four resins (**12a–d**) were obtained. Thiolate cleavage[11] of a sample of each released the corresponding Boc protected primary amines (**2a–d**) in good yield after flash chromatography. Each of the four resins were then treated with three diverse alcohols that, on cleavage, gave the secondary amines (**4a–l**). Interestingly amine (**4i**) and (**4j**) afforded the same product in similar yield and purity showing the order of reaction to be unimportant.

In conclusion, we have developed a versatile amine releasing linker that enables the direct elaboration of



Scheme 2. *Reagents and conditions*: (a) i. Na_2S_2, DMSO, EtOH, 2 h, rt, 51%, ii. Cl_2, CH_2Cl_2, AcOH, H_2O, 3 h, rt, 62%; (b) MeOH, ammonia, 2 h, rt, 98%; (c) i. (**7**), PyBOP, HOBt, DIPEA, DMF, CH_2Cl_2, 18 h, rt, 100%; (d) $(Boc)_2O$, Et_3N, CH_2Cl_2, 2 h, rt, 100%.

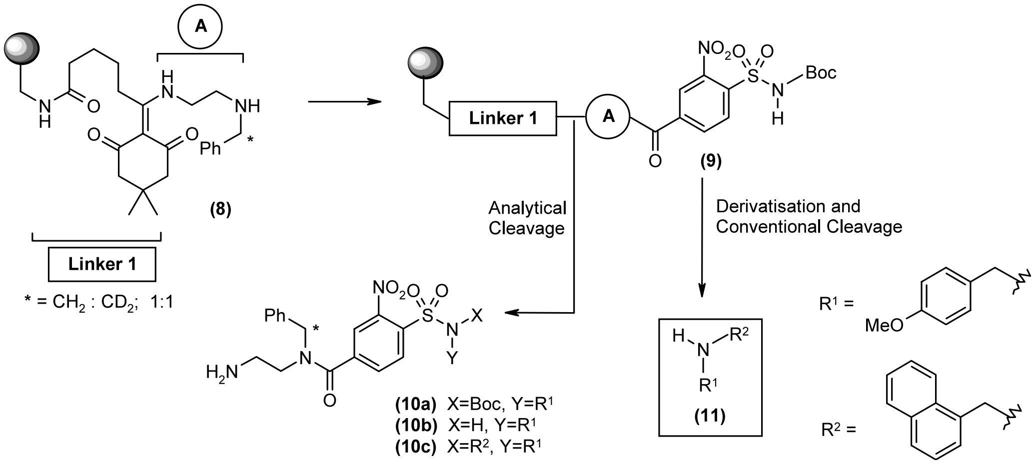
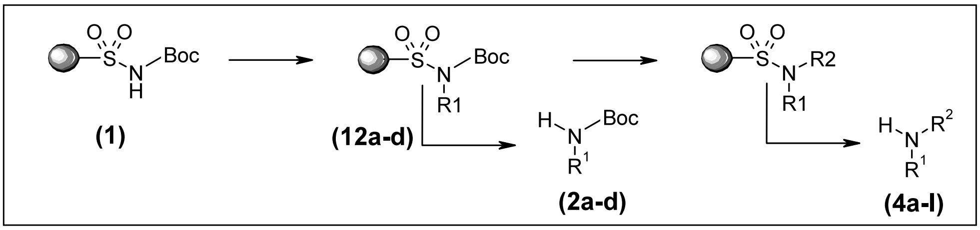
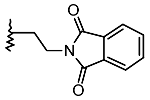
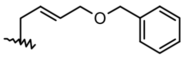
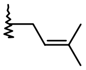
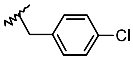
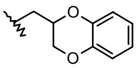
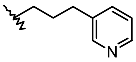
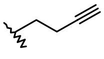
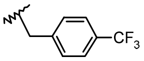
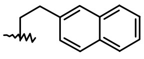
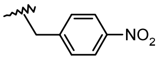
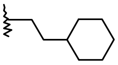
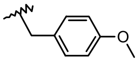
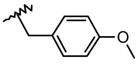
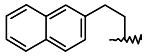
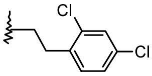
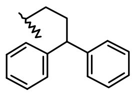


Figure 1. Analytical construct features. The construct contains an analytical enhancer (A) including a 1:1 mixture of hydrogen and deuterium isotopes to aid MS analysis (peak splitter) and a secondary amine to aid ESI positive mode ionisation (MS sensitiser). Analytical cleavage (2% hydrazine in DMF) releases the amine-tagged analytical fragment. Conventional cleavage (thiol, base) releases the target compounds.

Table 1. Preparation of an array of primary and secondary amines



Entry	R^1	R^2		Yield[a] NR^1R^2	Purity (^1HNMR)
a		Boc	2a		>95
b			4a	48	
c			4b	56	
d			4c	26	
e		Boc	2b		>95
f			4d	49	
g			4e	49	
h			4f	21	
i		Boc	2c		>95
j			4g	58	
k			4h	59	
l			4i	63	
m		Boc	2d	50	>95
n			4j	46	
o			4k	47	
p			4l	52	

[a]Cleavage conditions and workup procedures are not optimised. [b]Compounds (**4a-d**) were purified by flash chromatography.

both primary and secondary amines directly on resin.

This represents a significant advantage over the previously published *o*-nitrobenzenesulfonamide linker.

Acknowledgements

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