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A convenient one-pot preparation and applications of high loading benzhydrylamine solid phase linkers

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Abstract—A rapid and convenient one-pot route to solid supported benzhydrylamine linkers with high chemical loading is described. Such linkers possess differing levels of acid lability, which could be exploited in solid phase synthesis applications. They have also been utilised to prepare novel and potentially useful N-methylated derivatives. We also report an effective on-resin purification strategy for reductive amination, which is facilitated by the varying acid lability of resin-linked secondary amines or tertiary amine by-products.

The solid phase preparation of combinatorial compound libraries has become an important tool in organic synthesis.[1] Within this field, solid supported linkers of many types have been extensively employed in the construction of a wide variety of organic molecules.[2] The polymer bound 4-methoxybenzhydrylamine linker **1** (Fig. 1) and related constructs have extensive applications in solid phase synthesis. Linkers of this type have been employed in the solid phase preparation of peptides, ureas, amines, secondary amides and sulfonamides, which can be efficiently obtained in high purity by mild acid-mediated cleavage and washing.[3–5] Alternatives to **1** can include polymer supported Rink Amide **2**[6] and Sieber Amide **3**[7] (Fig. 1); however, these and others generally offer significantly lower levels of chemical loading as compared to **1**. Further, the potential instability of the ether linkages in **2** and **3** to acidic conditions has been previously noted.[4]

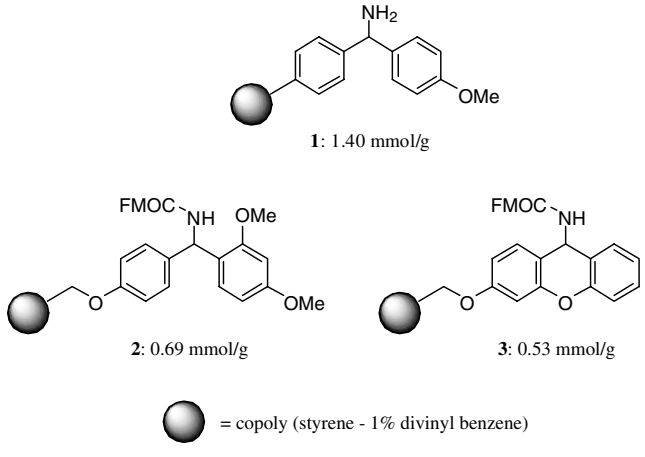

Figure 1. Structures and typical loadings of benzhydrylamine type linkers **1**–**3**.

During a medicinal chemistry project whose aim was to prepare a medium size library of protein kinase inhibitors using IRORI MicroKan technology,[8] we required a rapid, scaleable route to the high loading polystyrene-supported benzhydrylamine linker **1**. To the best of our knowledge, the commercial availability of **1** is currently limited to support on polystyrene beads of size 200–400 mesh (38–75 μm); this renders it unsuitable for use in MicroKans, whose mesh walls contain pores of diameter 74 μm.[9] Successful solution phase chemistry investigations (utilising benzhydrylamine as a surrogate for **1**) convinced us to investigate approaches to this linker on suitably sized polystyrene particles. Here, we would like to report the successful outcome of these studies, which have resulted in the preparation of new and currently available variants of **1**, and some brief observations on the utility and acid lability of these linkers in solid phase chemistry applications.

Keywords: Solid phase; Linkers; Benzhydrylamines; Cleavage.
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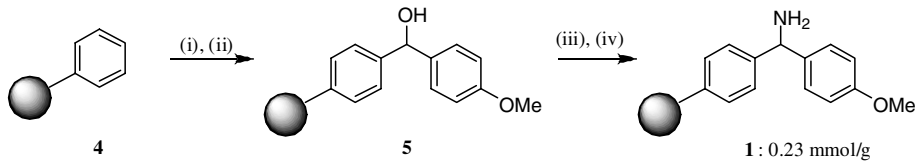
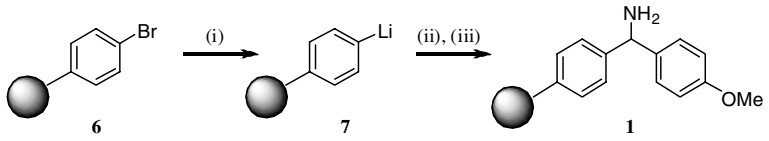


Scheme 1. Reagents and conditions: (i) 1 equiv *p*-anisoyl chloride, 2.5 equiv $FeCl_3$, CH_2Cl_2, rt, 18 h; (ii) 10 equiv $NaBH_4$, DMF–MeOH 5:1, rt, 18 h; (iii) 5 equiv phenyl carbamate, AcOH–H_2SO_4, 98:2, rt, 18 h; (iv) 10 equiv LiOH, dioxane–H_2O, 50 °C, 3 h.

Table 1. Reagents and conditions: (i) 4 equiv ^{n}BuLi, toluene 60 °C, 3 h; (ii) 10 equiv 4-$MeOC_6H_4CN$, toluene, rt, 20 min; (iii) add 20% v/v MeOH, then 20 equiv $NaBH_4$, rt, 30 min



50-100 mesh
1.94 mmol/g

1.52-1.78 mmol/g

Entry	Scale (g)	Steps (i)–(ii) solvent	Step (iii) solvent	Loading (mmol/g)
1	2	THF	DMF–MeOH 5:1	1.52
2	2	THF	Add 20% MeOH	1.55
3	2	Toluene	Add 20% MeOH[a]	1.57 (1.78)
4	10	Toluene	Add 20% MeOH	1.66

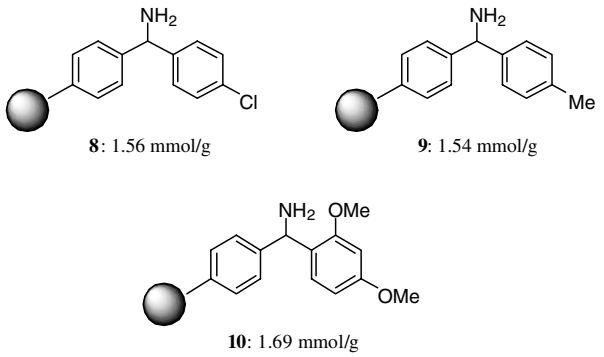
[a] Could also be performed using BH_3–pyridine complex as the reducing agent—loading in parentheses.

Our first approach to the preparation of polymer bound linker **1** was based upon the known Friedel–Crafts acylation and reduction of polystyrene **4**,[10,11] as shown in Scheme 1. As expected, both these steps appeared to proceed smoothly to generate alcohol **5**, as implied by a positive alcohol test.[12] We then briefly examined the transformation of **5** into the required linker **1** via a two-step protocol.[13] A Kaiser test for the presence of a primary amine group[12] suggested that **1** had been formed, but subsequent elemental analysis revealed a disappointing chemical loading of 0.23 mmol/g. It seems likely that the aqueous, polar conditions for this transformation are unsuitable for use in a solid phase context, due to their ineffective swelling of the resin. We also attempted the preparation of **1** via a Leuckart reaction,[1] but in our hands this also resulted in a poor functional loading.

Seeking an alternative approach to **1**, we turned to the regioselective lithiation of bromopolystyrene **6**.[4,14] We were pleased to find that by quenching intermediate **7** with 4-methoxybenzonitrile[15] and reducing the imine in situ, the desired linker **1** could be prepared with a substantially improved chemical loading (Table 1).[16] The progress of these reactions were accompanied by changes in the colour of the resin. The polystyrene was observed to change from yellow **7** to deep red on addition of the nitrile, and back to yellow **1** on reduction. It is noteworthy that no washing of the resin was necessary between the reaction steps.

A short study of the reaction conditions showed that toluene could be replaced by THF in the lithiation and quenching steps (Table 1, entries 2–3). The reduction still required a change of solvent (entry 2) or addition of methanol as before (entry 3), in order to help to dissolve the sodium borohydride. The reduction step could be performed equally well using borane–pyridine as the reducing agent. These modifications generated **1** with similarly high levels of chemical loading, according to elemental analysis. Encouragingly, this was maintained during a larger scale process (entry 4), which indicates that this is a robust and reliable procedure. In addition, by changing the aryl nitrile component, we were able to prepare similar quantities of **8**, **9**[17] and **10** with comparably high loadings (Fig. 2).

The differing substitution patterns in linkers **1** and **8**–**10** are likely to lead to changes in acid lability. To assess this, each resin was capped with tosyl chloride and the resulting sulfonamides cleaved with 50% TFA in dichloromethane. Quantification of the chemical yield of sulfonamide **11** by NMR spectroscopy (Table 2) showed



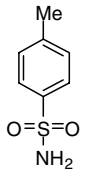
8: 1.56 mmol/g

9: 1.54 mmol/g

10: 1.69 mmol/g

Figure 2. Structures of alternative linkers **8**–**10**.

Table 2. Relative acid labilities of **1** and **8**–**10** by yield of sulfonamide **11**

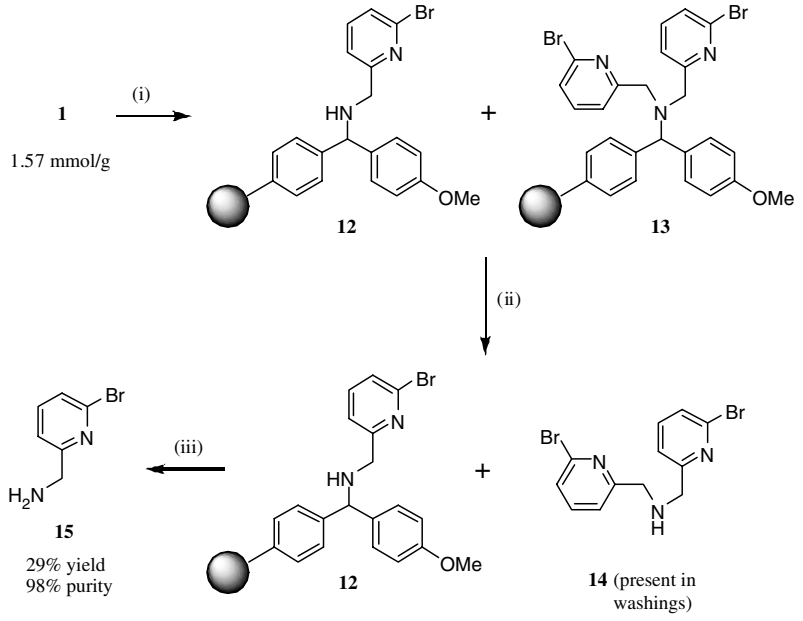


11

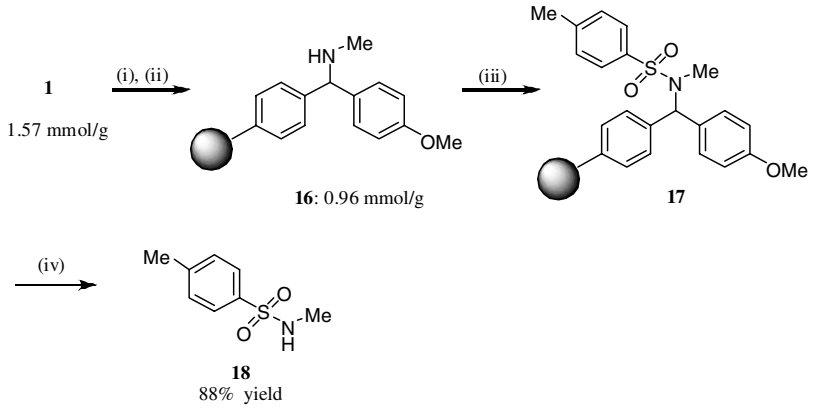
Entry	Linker	Chemical yield of **11** (%)
1	**1**	60
2	**8**	3
3	**9**	89
4	**10**	45

that linker **9** (entry 2) had a significantly higher stability to acid. This could be explained by its lower basicity due to the electron-withdrawing nature of the 4-chlorine substituent.[18] Such properties might be exploited in solid phase synthesis applications where acidic conditions are necessary.[5]

Different types of resin-bound compound should also possess differing levels of acid lability on the same resin. We sought to apply this in the context of a reductive amination reaction, which has been extensively utilised for the functionalisation of amine resins. To circumvent the problem of over-alkylation,[19] a simple purification strategy was designed to take advantage of the higher acid lability of tertiary amine by-products as compared to secondary amines. Hence, the reductive amination of linker **1** with 2-bromo-6-formylpyridine gave a 3:1 ratio of **12** and **13** (Scheme 2), determined by complete removal from a sample of the resin by standard acid-mediated cleavage. However, when this mixture was treated for a short time with dilute acid and rinsed,



Scheme 2. Reagents and conditions: (i) 2-bromo-6-formylpyridine, AcOH, 1,2-DCE, $NaBH(OAc)_3$, rt, 48 h; (ii) TFA–CH_2Cl_2–H_2O 5:94:1, rt, 2 h; (iii) TFA–CH_2Cl_2–H_2O 49:50:1, rt, 2 h.



Scheme 3. Reagents and conditions: (i) 20 equiv $ClCO_2Me$, 2 equiv Et_3N, THF, rt, 3 h; (ii) 3 equiv $LiAlH_4$, THF, rt, 4 h; (iii) 5 equiv TsCl, $CHCl_3$–py 5:1, 50 °C, 48 h; (iv) TFA–CH_2Cl_2–H_2O 48:48:1, rt, 1 h.

the filtrates were observed to contain only **14** from the unwanted by-product **13**. The remaining resin-bound secondary amine **12** could be then further functionalised, or cleaved under standard conditions to give product **15** in excellent purity.

A further application of this type of linker could be derived from the preparation of *N*-alkyl derivatives. We found that methylation of **1** could be achieved by means of a two-step process as shown in Scheme 3.[20] Introduction of a carbamate motif was followed by reduction to give *N*-methyl linker **16**, albeit with a reduced loading. Sulfonylation and cleavage from the resin using standard procedures gave secondary sulfonamide **18** in a good yield and excellent purity. We anticipate that **16** could also find utility in the preparation of secondary amines, by means of a further alkylation reaction followed by cleavage.

In summary, we have developed a short and robust procedure for the preparation of polymer supported benzhydrylamine linkers on beads suitable for use in the IRORI MicroKan system. The preparation utilising inexpensive and readily available starting materials is amenable to scale-up and has been applied to the preparation of currently available and useful new analogues. We have also expanded the utility of this type of linker in solid phase chemistry applications, which should allow the exploration of novel routes to several important compound classes.

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16. *Preparation of* **1**. Bromopolystyrene **6** (2.05 g, 1.94 mmol/g, 50–100 mesh) was stirred in anhydrous toluene (15 ml). The solvent was degassed and backfilled with nitrogen. When the resin was fully swollen (15 min), ^{n}BuLi (6.4 ml, 2.5 M in hexanes) was added and the reaction was heated to 60 °C for 3 h. 4-Methoxybenzonitrile (5.30 g, 39.8 mmol, 10 equiv) was added and the reaction mixture stirred for 10 min. Methanol (2 ml) and sodium borohydride (2.80 g, 20 equiv) were added and the suspension was stirred for a further 30 min at room temperature. The resin was collected by filtration and washed with methanol (5 ml), THF (5 ml) and DCM (3×5 ml) and dried overnight in a dessicator to give a pale yellow solid (2.38 g). Elemental analysis: Br 0.03%, N 2.21% (loading 1.57 mmol/g). The other resins prepared using this method showed comparably low levels of remaining bromine.
17. Resin **9** is commercially available (e.g., Novabiochem, Merck Biosciences, UK).
18. A similar effect has been reported for closely related trityl resins; for example, see: Park, J. G.; Langenwalter, K. J.; Weinbaum, C. A.; Casey, P. J.; Pang, Y.-P. *J. Comb. Chem.* **2004**, *6*, 407–413.
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20. *Preparation of* **16**. Resin **1** (200 mg, 0.32 mmol) was swollen in THF (3 ml) for 30 min. Triethylamine (0.12 ml, 0.66 ml) and methyl chloroformate (0.50 ml, 6.6 mmol) were added dropwise and the reaction agitated for 4 h. The resin was filtered and rinsed (DCM–MeOH 9:1, 4×3 ml). A Kaiser test indicated that all the primary amine had been consumed. The resin was re-dissolved in THF (3 ml), $LiAlH_4$ (40 mg) added and the mixture left at room temperature for 4 h. The resin was filtered and rinsed ($CHCl_3$, MeOH, DMF–H_2O 4:1 (×2), MeOH, $CHCl_3$ (×4)). Elemental analysis: N 1.35% (loading 0.96 mmol/g).