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Monoacylation of unprotected symmetrical diamines with resin-bound benzoic acids

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Abstract—A protocol for monoacylation of unprotected symmetrical diamines with a resin-bound benzoic acid is described. The nature of the resin (gel-based polystyrene vs highly crosslinked macroporous polystyrene) was found to play a minor role in acylation selectivity. Rather, the concentration of the diamine dictates the ratio of mono- and diacylated products. Thus, by employing a high concentration of symmetrical diamine (e.g., 1 M, 20 equiv), monoacylation can be selectively achieved for a variety of unprotected symmetrical alkyl and aryl diamines.

1. Introduction

The backbone amide linker (BAL), originally designed for synthesis of peptides, has found widespread application in preparation of small organic molecule arrays for drug discovery.[1] The most commonly used BALs are tris(alkoxy)benzaldehyde based linkers that allow the anchoring of substrates by convenient reductive amination and the release of the final products by treatment with concentrated trifluoroacetic acid (TFA).[1,2] A few functionalized resins with tris(alkoxy)benzaldehyde based linkers (e.g., **A**, **B**, and **C** in Fig. 1) have been conveniently prepared[3,4] and successfully used in the synthesis of a number of small molecule arrays including amide, sulfonamide, urea, amines, hydroxamate, and heterocycles, etc.[5]

Efficient synthesis of resin-bound benzamides **5** from resin-bound benzoic acids **1** and diamines **2** was key for preparation of several target-class-directed arrays (Scheme 1, where L represents any structural moiety between BAL resins **A**–**C** and benzoic acid, and formula **2** represents 1° and 2° cyclic/acyclic symmetrical diamines). The conventional way to prepare benzamides **5** is to react monoprotected symmetrical diamines (**3**, where PG is an appropriate protecting group) with **1** followed by *N*-deprotection of resin-bound intermediates **4**. While this method may often work well, it lacks efficiency and large-scale synthesis of monoprotected symmetrical diamines **3** is often tedious. Alternatively, direct acylation of unprotected symmetrical diamines **2** with resin-bound acids **1** would save two steps (protection and deprotection) but could potentially result in

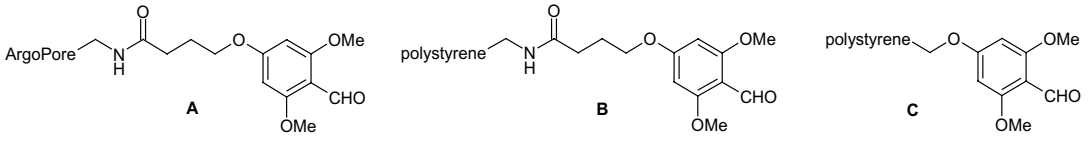

Figure 1. BAL-functionalized resins.

Keywords: Monoacylation; Diacylation; Crosslinking; Symmetrical diamines; Resin comparison; Concentration effect; Solid phase reaction.
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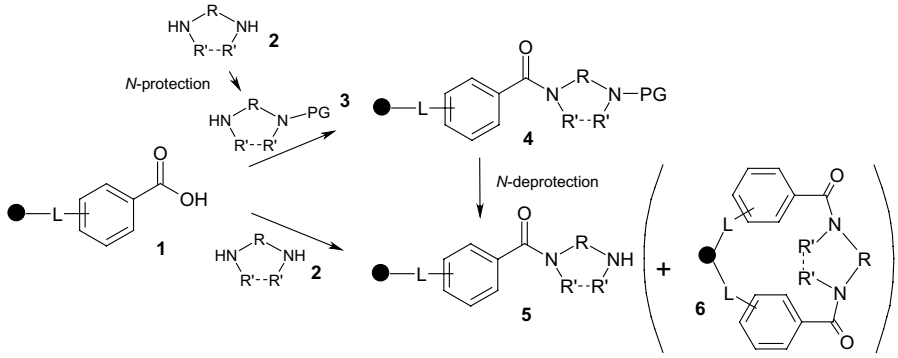


Scheme 1. Synthetic options for preparation of resin-bound **5**.

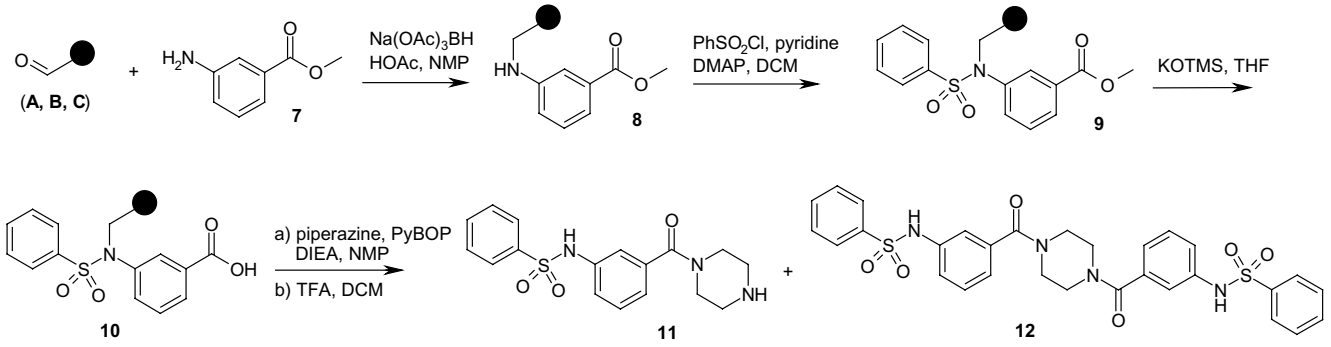
double acylation of diamines **2** leading to undesired crosslinking products **6**. The situation described here is actually quite common as byproducts derived from crosslinking events are also frequently encountered when symmetrical diamines react with other resin-bound electrophiles (alkyl halides, aldehydes etc.).[6] If undesired crosslinking products **6** can be successfully eliminated or minimized, direct acylation of unprotected symmetrical diamines **2** will be an efficient and attractive way to prepare resin-bound benzamides **5**. It is often assumed that diacylation or crosslinking can be overcome by using an excess of diamine and/or a rigid, lower-loaded, non-swelling resin ('site isolation'),[7] but systematic studies are seldom reported. In this paper, we wish to report a more systematic study concerning direct monoacylation of unprotected symmetrical diamines **2** with resin-bound carboxylic acids.

2. Results and discussion

2.1. Resin effects

While gel-based 1% cross-linked polystyrene resin exhibits high loading and robust solvent swelling characteristics, highly cross-linked (>10%) macroporous polystyrene resins, such as ArgoPore®, have a more rigid, uniform pore structure that is much less prone to swelling.[8] We reasoned that double acylation (conversion of **5** to **6**) might be minimized by use of this rigid, and lower-loaded ArgoPore® resin (via site isolation). To our surprise, considerable crosslinking was still observed during the synthesis of an array using ArgoPore® BAL-resin (**A**). This observation prompted us to examine in greater detail the effect of the resin type (gel vs macroporous) on acylation selectivity. A direct comparison of ArgoPore® BAL-resin (**A**) and 1%-crosslinked polystyrene BAL-resins (**B**, **C**) was conducted and the effect of linker length (spacer) was examined by comparison of polystyrene BAL-resins **B** and **C**.

Resin-bound benzoic acids **10A**–**C** were prepared by loading methyl 3-aminobenzoate **7** onto resins **A**–**C** via a reductive amination, sulfonylation, and saponification sequence (Scheme 2).[9] Pre-treatment of resins **10A**–**C** with excess piperazine followed by subsequent activation of the resin-bound acid (3 equiv PyBOP; 6 equiv DIEA) provided mixtures of mono- and diacylated products after TFA cleavage (**11**, **12**, respectively).[10,11] The ratios of products **11** and **12** were determined by LC-MS[12] and the results are shown in Table 1. At a given piperazine equivalent and concentration (i.e., 4 equiv piperazine, 0.015 M), resins **10A** and **10B** yielded nearly identical ratios of mono- and diacylated products **11**:**12** (25:75 vs 23:77, respectively). Product ratios derived from resins **10A** and **10B** at two additional equivalents/concentrations were quite similar as well (60:40 vs 63:37 and 79:21 vs 85:15). Thus, under the conditions explored here, use of the macroporous resin **10A** did not significantly reduce the amount of



Scheme 2. Solid-phase synthesis of products **11** and **12**.

Table 1. Mole ratio of mono- and diacylated products (**11**:**12**) for resin **A**, **B**, and **C**

Benzoic acids	Loading[a] (mmol/g)	Piperazine		Mole ratio[b]
		Equiv	Conc. (M)	**11**:**12**
10A	0.58	4	0.015	25:75
		50	0.02	60:40
		50	0.05	79:21
10B	0.96	4	0.015	23:77
		50	0.02	63:37
		50	0.05	85:15
10C	1.18	4	0.015	8:92
		50	0.02	51:49
		50	0.05	77:23

[a] Based on the loading of resin-bound ester **9** determined gravimetrically following cleavage of corresponding sulfonamide product.
[b] Mole ratio calculated according to LC-MS UV area ratio corrected by calibration factor (1.72 * UV area for **11**:UV area for **12**).[12]

diacylated product **12** relative to that of the gel-based resin **10B**. This result is surprising as intuition suggests that the more rigid matrix and the lower loading of the macroporous resin should tend to increase site isolation and thus decrease diacylation events (formation of **6** from **5**, Scheme 1). Further, one might expect crosslinking events to be more common as the length of spacer (base resin to tris(alkoxybenzyl) anchor point) increases from resin **10C** to **10B** (owing to less site isolation). However, a second observation from Table 1 is the fact that at each data point, resin **10C** (shorter spacer) consistently provided more diacylated product **12** compared to use of resin **10B** (longer spacer). This observation could be the result of multiple effects such as ~20% higher resin loading of resin **10C** vs **10B** (less site isolation in **10C**) or an impact of the spacer (i.e., spacer length/composition can impact resin swelling properties or propensity toward crosslinking events). A key observation from Table 1 is that increased piperazine concentrations (though not equivalents used) led to improved ratios of mono- and diacylated products for all three resins (**10A**–**C**). This finding encouraged us to examine in detail the effects of concentration on acylation selectivity.

2.2. Concentration effects

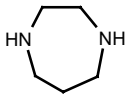
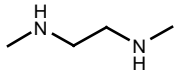
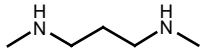
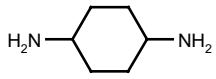
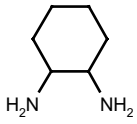
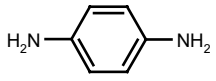
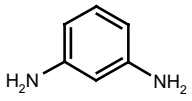
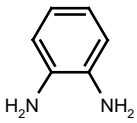
Concentration studies with BAL resin **C** were then undertaken.[13] As expected for a bimolecular reaction and as demonstrated in Table 2, it is the piperazine concentration that plays a critical role in the acylation selectivity. For the same amount of piperazine (e.g., 50 equiv to resin-bound benzoic acid), when the concentration of piperazine increased from 0.005 to 0.5 M, the mole ratio of **11**:**12** changed dramatically from 10:90 to 98:2, respectively. In contrast, when the concentration of piperazine was kept constant at 1 M, the amount of piperazine employed (10–100 equiv) had essentially no effect on the ratio of mono- and diacylated products **11**:**12**. This result is not difficult to understand. Assuming incomplete site isolation, activated resin-bound benzoic acid **10C** can react with not only free piperazine in solution but also with any monoacylated product **11C** that is in sufficiently close proximity. The competition will favor formation of **11C** if the local concentration of free piperazine is high. On the other hand, crosslinking

Table 2. Ratio of mono- and diacylated products (**11**:**12**) under different piperazine concentrations and equivalents for resin **C**

Entry	Piperazine		Mole ratio[a]
	Equiv	Conc. (M)	**11**:**12**
1	50	0.005	10:90
2	50	0.01	19:81
3	50	0.02	51:49
4	50	0.05	77:23
5	50	0.1	91:9
6	50	0.2	96:4
7	50	0.5	98:2
8	10	1.0	97:3
9	20	1.0	98:2
10	50	1.0	98:2
11	100	1.0	98:2

[a] Mole ratio calculated according to LC-MS UV area ratio corrected by calibration factor (1.72 * UV area for **11**:UV area for **12**).[12]

Table 3. Product ratios (**M**:**D**) after reaction of **10C** with different diamines (1 M, 20 equiv)

Reaction entry	Diamine **2**	Mole ratio **M**:**D**[a,b,c]
13		>99:1
14		98:2
15		96:4
16		96:4
17		98:2
18		>99:1
19		97:3
20		>99:1

[a] **M** represents the **M**onoacylated product analogous to **11**. **D** represents the **D**iacylated product analogous to **12**.
[b] Structures of all products were confirmed by NMR and MS analysis.
[c] Mole ratio calculated according to LC-MS UV area ratio corrected by calibration factor (1.72 * UV area for **11**:UV area for **12**).[12]

events will dominate (formation of diacylated product **12C**) if the local concentration of piperazine is low[14] and formation of the macrocyclic ring is energetically favored.

2.3. Application to other symmetrical diamines

To explore the scope of this monoacylation protocol, eight other symmetrical diamines **2** were employed using the same acylation protocol to react with **10C**.[10] The ratios of mono- and diacylated products (**13**–**20M**, **13**–**20D**, respectively), determined after reaction of activated **10C** with different diamines **2**, are summarized in Table 3. Employing high concentration of diamines (1 M, 20 equiv), all reactions provided ratios of mono- and diacylated products in excess of 96:4 based on LC-MS UV analysis. These product ratios are synthetically useful. We have successfully exploited these conditions numerous times for efficient synthesis of small molecule arrays.[15]

3. Conclusion

We have described how to achieve efficient monoacylation of unprotected symmetrical diamines with a resin bound benzoic acid. The nature of the resin (gel-based polystyrene vs highly crosslinked macroporous polystyrene) was found to play a minimal role in acylation selectivity. Rather, concentration of the diamine **2** was primarily observed to dictate the ratio of mono- and diacylated products. Thus, by employing a high concentration of symmetrical diamine (e.g., 1 M, 20 equiv), monoacylation can be selectively achieved for a variety of unprotected symmetrical alkyl and aryl diamines. In our laboratory, we have since exploited these conditions to synthesize over 12,000 compounds.

References and notes

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4. In this work, resin **A** was prepared from ArgoPore® CH_2NH_2 resin (Argonaut Technologies Inc., Part Number 800160, average bead diameter 134 μm, loading 1.22 mmol/g, average crosslinking 50%); Resin **B** was prepared from IRORI UniSphere® 200 resin (supplied by Polymer Laboratories, Part No. USR200-02, loading 1.56 mmol/g, crosslinking 1%); Resin **C** was purchased from Polymer Laboratories, Part Number: 1466–6689; 150–300 μm, 1.5 mmol/g, crosslinking 1%.
5. For example, see: (a) Yamashita, D. S.; Dong, X.; Oh, H.-J.; Brook, C. S.; Tomaszek, T. A.; Szewczuk, L.; Tew, D. G.; Veber, D. F. *J. Comb. Chem.* **1999**, *1*, 207–215; (b) Forns, P.; Sevilla, S.; Erra, M.; Ortega, A.; Fernandez, J.-C.; Figuera, N.; Fernandez-Forner, D.; Albericio, F. *Tetrahedron Lett.* **2003**, *44*, 6907–6910; (c) Ngu, K.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 7088–7089; (d) Gray, N. S.; Kwon, S.; Schultz, P. G. *Tetrahedron Lett.* **1997**, *38*, 1161–1164.
6. Jin J.; Wang, Y.; Cai, M.; Budzik, B., unpublished results. For example, (a) the reaction of BAL resin **C**-bound benzyl bromide with piperazine led to 32% of double alkylation product; (b) the reductive amination of BAL resin **C**-bound benzaldehyde with piperazine afforded 30% *N*,*N*′-dialkylated product.
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9. The product cleaved from **10A**, **10B**, and **10C** was the same (3-[(phenylsulfonyl)amino]benzoic acid) and essentially pure (100% by LC-MS): **MS** (ESI): 555 (M_2H^+); 278 (MH^+), 260 (MH^+-18).
10. A typical acylation experiment: 30 mg of **10C** (1.18 mmol/g, 0.0354 mmol) was added into a vial containing a solution of 61 mg piperazine (0.71 mmol) in *N*-methyl pyrrolidinone (NMP) (0.71 mL), followed by 37 μL of DIEA (0.21 mmol) and 55 mg of PyBOP (0.107 mmol). The mixture was shaken at RT overnight and the resin was washed with NMP, DCM, MeOH, and DCM, respectively, and dried under vacuum. About 2 mg of resin was cleaved with 0.5 mL of 50% TFA in DCE for 20 min. 0.2 mL of TFA solution was taken and evaporated to dryness. The residue was dissolved in 0.5 mL of MeOH for LC-MS analysis.
11. Characterization of **11**: ^{1}H NMR (DMSO-d_6) δ 3.12 (broad, 4H), 3.36 (broad, 2H), 3.73 (broad, 2H), 7.10 (d, J = 7.65 Hz, 1H), 7.13 (s, 1H), 7.16 (d, J = 8.22 Hz, 1H), 7.32 (t, J = 7.85 Hz, 1H), 7.55 (t, J = 7.86 Hz, 2H), 7.61 (t, J = 7.38 Hz, 1H), 7.75 (d, J = 7.34 Hz, 2H), 8.93 (s, 1H), 10.52 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 42.5, 118.5, 121.3, 122.7, 126.7, 129.4, 129.6, 133.1, 135.7, 137.8, 139.2, 168.4. **MS** (ESI): 691 (M_2H^+); 346 (MH^+). Characterization of **12**: ^{1}H NMR (DMSO-d_6) δ 2.99 (broad, 2H), 3.20 (broad, 2H), 3.49 (broad, 2H), 3.67 (broad, 2H), 7.05 (s, 2H), 7.06 (d, J = 7.56 Hz, 2H), 7.18 (d, J = 8.42 Hz, 2H), 7.32 (t, J = 7.89 Hz, 2H), 7.50 (broad, 6H), 7.74 (d, J = 6.85 Hz, 4H). ^{13}C NMR (DMSO-d_6) δ 118.3, 121.2, 122.7, 126.7, 129.3, 129.6, 133.0, 136.4, 137.8, 139.1, 168.4. **MS** (ESI): 605 (MH^+).
12. Calibration factor determination: Equimolar amounts of purified **11** and **12** were mixed and dissolved in methanol. UV absorbance of **11** and **12** in methanol was measured three times at four different concentrations (0.2, 0.3, 0.5, and 1.0 μmol). The UV area ratios of **11**:**12** were then averaged.
13. BAL resin **C** was chosen for further study because of its higher loading and availability.
14. Local concentration may be different from bulk concentration if the reaction is quick and mass transportation through the resin is slow.
15. Wang, Y.; Jin, J.; Wang, F., unpublished results.