

# Application of a New Solid-Phase Resin: Benzamide *ortho*-Lithiation and the Synthesis of a Phthalide Library

Patrick Garibay,<sup>a</sup> Patrick H. Toy,<sup>b</sup> Thomas Hoeg-Jensen<sup>a</sup>, Kim D. Janda<sup>b,\*</sup>

<sup>a</sup>Novo Nordisk A/S, Novo Alle 6BS.58, DK-2800 Bagsvaerd, Denmark

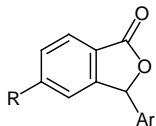
<sup>b</sup>Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037

Received 6 July 1999

**Abstract:** The utility of new polytetrahydrofuran cross-linked polystyrene resins is demonstrated through the solid-phase synthesis of a phthalide library. The phthalides are synthesized via directed *ortho*-lithiation of resin bound benzamides and isolated via cyclative cleavage.

**Key words:** solid-phase synthesis, resin, *ortho*-lithiation, phthalide

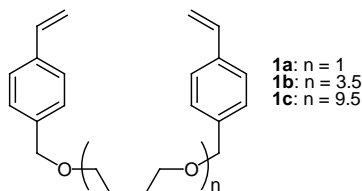
The synthetic utility of the directed *ortho*-metallation (DoM) reaction is well documented.<sup>1</sup> Despite the renewed interest in the adaptation of solution-phase organic reactions to the solid-phase,<sup>2</sup> there are only two reported examples of DoM chemistry applied on a solid support: (1) The lithiation of 1-hydroxyimidazole with *n*-BuLi.<sup>3</sup> In this case, the increased acidity of the proton on the heterocycle allowed for selective deprotonation without interference caused by resin deprotonation, which is known to occur.<sup>4,5</sup> (2) A single example of the lithiation of a phenyl ether.<sup>6</sup> The development of a general procedure for the solid-phase DoM of the commonly used benzamide moiety would greatly extend the utility of this type of chemistry. Furthermore, the directed lithiation of benzamides could provide convenient access to the phthalide class of compounds (Figure 1). Using such a strategy, the solid-phase DoM of benzamides to synthesize a library of phthalide molecules would have two noteworthy features: (1) The trapping step is amenable to the use of a variety of electrophiles. (2) The amide functionality acts as both the directing group for metalation and as the linker to the resin. The result of this combination is that cyclic cleavage of only the desired product would be observed.



**Figure 1** General structure of phthalide library compounds.

We have recently introduced a new class of resins designed specifically for solid-phase organic synthesis that are based on polytetrahydrofuran (PTHF) cross-linkers **1a-c** (Figure 2).<sup>7</sup> Our decision for utilizing this type of cross-linking element was based upon the following considerations: (1) The desire to create a resin interior that is

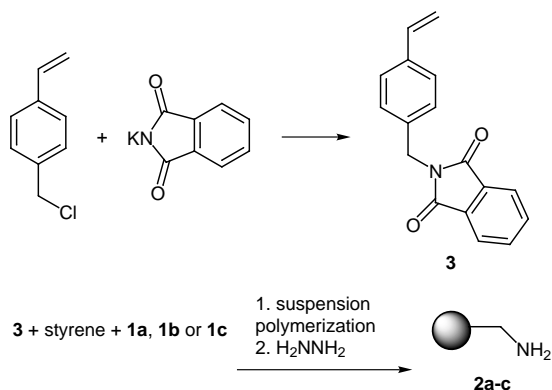
more “organic solvent-like” than that of divinyl benzene (DVB) cross-linked resins. (2) Anticipation that the flexible PTHF cross-linkers could result in better site accessibility as compared to relatively rigid DVB cross-linked resins. Herein we report the utilization of the PTHF cross-linked resins in the synthesis of a phthalide library via a benzamide *ortho*-lithiation reaction.



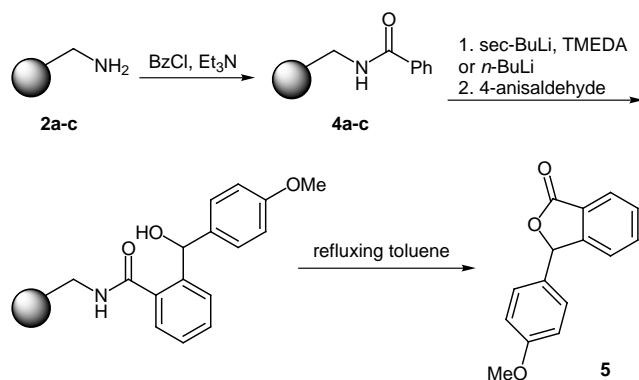
**Figure 2** Polytetrahydrofuran-based resin cross-linkers.

Traditionally aminomethyl resins are prepared by derivatization of preformed resin beads.<sup>8</sup> We chose an alternative method that involves the incorporation of a functionalized monomer into the polymerization reaction. It was deemed that this procedure would result in resins of more highly defined composition. Thus, aminomethyl resins **2a-c** were prepared by suspension copolymerization of **1a-c**, **3** and styrene followed by removal of the phthalimide protecting group (Figure 3). We believe that in the future this process of polymerization of functional monomers will become a valuable alternative to traditional bead derivitization. As previously reported,<sup>7</sup> we found that for resins cross-linked with **1a-c**, at least 5 mole percent cross-linking was required to ensure resin stability to *n*-BuLi. Therefore resins **2a-c** are all 5 percent cross-linked. It should be noted that incorporation of **3** into the polymerization process allowed for direct attachment of the requisite aryl molecule to the resin without use of an intermediary spacer or linker group.

Resins **2a-c** were treated with benzoyl chloride and triethylamine to yield **4a-c**. Sequential treatment of **4a-c** with tetramethylethylenediamine (TMEDA) and *sec*-BuLi was followed by addition of 4-anisaldehyde. Product **5** was obtained by treatment of the resins with refluxing toluene (Table 1). It should be noted that commercial DVB cross-linked polystyrene (PS) provided lower yield than did resins **2a-c**. Tentagel-NH<sub>2</sub> was also examined, but only trace amounts of contaminated **5** could be isolated.



**Figure 3** The preparation of phthalimide monomer **3** and amino-methyl resins **2a-c**.

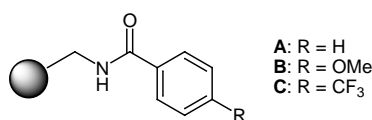


**Figure 4** The solid-phase synthesis of **5**.

**Table 1** Yields of the solid-phase synthesis of **5**.

Resin	Loading (mmol/g)	Yield of <b>5</b> (%)
<b>2a</b> (5%- <b>1a</b> )	0.76	37
<b>2b</b> (5%- <b>1b</b> )	0.73	34
<b>2c</b> (5%- <b>1c</b> )	0.68	43
PS (1%-DVB)	1.25	21

Since resin **2c** afforded the highest yield of **5**, it was chosen as the support for the library synthesis. During further optimization of the reaction, it was found that higher yields were obtained when *n*-BuLi was used in the absence of TMEDA. To generate a diverse library, resin **2c** was treated with benzoyl chloride, 4-methoxybenzoyl chloride and 4-trifluoromethylbenzoyl chloride to afford resins **A**, **B**, and **C**, respectively (Figure 5). These three electronically different benzamides were lithiated with *n*-BuLi and reacted each with 8 aromatic aldehydes to afford a 24 member library (Table 2). All compounds were characterized by <sup>1</sup>H-NMR and found to be greater than 95 percent pure. Furthermore, yields were comparable to what is observed in solution-phase chemistry.<sup>1</sup>



**Figure 5** Benzamide components for library synthesis.

In conclusion, a general method for the solid-phase DoM of benzamides has been developed and its versatility has been demonstrated through the generation of a high purity phthalide library. Furthermore, our new PTHF cross-linked resins have been shown to be suitable supports for this chemistry and they provide improved results compared to some of the most broadly used commercially available resins.

### Experimental

*N*-(4-vinylbenzyl)phthalimide (**3**).<sup>9</sup> A solution of 4-vinylbenzyl chloride (25.0 mL, 160 mmol), and potassium phthalimide (31.0 g, 168 mmol) in DMF (175 mL) was stirred at 60 °C for 16 h. The solvent was removed *in vacuo* and the resulting solid material was, and the resulting solid material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (250 mL). The organic solution was washed sequentially with 0.2 M NaOH (2 x 200 mL), water (200 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was recrystallized from ethanol to afford **3** (28.6 g, 68% yield), mp = 97–98 °C, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 4.83 (s, 2H), 5.22 (d, *J* = 10.6 Hz, 1H), 5.70 (d, *J* = 17.5 Hz, 1H), 6.67 (dd, *J*<sub>1</sub> = 17.5 Hz, *J*<sub>2</sub> = 10.6 Hz, 1H), 7.33–7.42 (m, 4H), 7.67–7.86 (m, 4H).

### General procedure for resin **2a-c** synthesis.

A solution of acacia gum (6.0 g) and NaCl (3.75 g) in water (150 mL) was placed in a 150 mL flanged reaction vessel equipped with a floating magnetic stirrer<sup>10</sup> and deoxygenated by purging with N<sub>2</sub>. A solution of **3** (2.00 g, 7.60 mmol), styrene (6.0 mL, 52.4 mmol), **1c** (2.65 g, 3.00 mmol), and benzoyl peroxide (0.15 g) in chlorobenzene (9 mL) was injected into the rapidly stirred aqueous solution. This mixture was heated to 85 °C for 16 h. The crude polymer was collected and washed in a Soxhlet extractor with water, THF and hexanes. The beads (8.52 g, 84%) were dried *in vacuo* and sieved to afford resins in 3 size ranges: 50–100 mesh (1.48 g, 15%), 100–200 mesh (3.49 g, 35%) and 200–400 mesh (1.66 g, 16%). The 100–200 mesh resin was suspended in refluxing 95% EtOH/H<sub>2</sub>NNH<sub>2</sub>·H<sub>2</sub>O (20:1, 40 mL) for 16 h. The resin was collected, washed with hot EtOH, H<sub>2</sub>O, dioxane, and MeOH (50 mL of each solvent) and dried *in vacuo*. The amine loading level was determined by Fmoc release assay.<sup>11</sup>

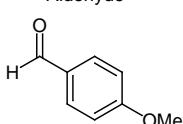
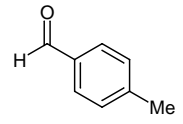
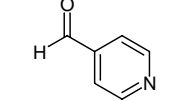
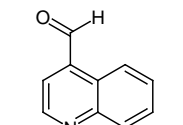
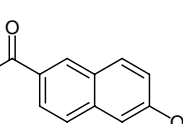
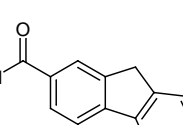
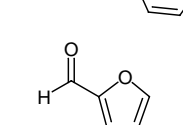
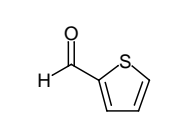
### General procedure for benzamide resins **A-C** synthesis.

Resin **2c** (1.0 g) was swollen in dry THF (15 mL) and treated with triethyl amine (5 eq.) and benzoyl chloride (5 eq.). After 1 h at room temperature, the resin was washed with THF, 1:1 THF/H<sub>2</sub>O, DMF, MeOH and ether (40 mL of each solvent) and dried *in vacuo*. Resins **A-C** were negative to a Kaiser amine test.<sup>12</sup>

### General procedure for phthalide library synthesis.

Resin **A** (0.126 mmol) was placed in a flame dried 50 mL round bottom flask equipped with a nitrogen inlet and a magnetic stirrer. Dry THF (10 mL) was added, the reaction mixture was cooled to 0 °C and *n*-BuLi (7 eq., 2.5 M in hexanes) was added. After 5 min the aldehyde (10 eq.) was added and the reaction mixture was allowed to stir at 0 °C for an additional 30 min. The reaction mixture was warmed to room temperature and after 1 h the resin was washed with THF, DMF, MeOH and ether (10 mL of each solvent). The re-

Table 2 Phthalide library yields

Aldehyde	Benzamide		
	A	B	C
	64	50	73
	58	56	79
	73	54	72
	43	59	66
	56	50	77
	41	50	81
	45	55	72
	64	53	78

sulting resin was refluxed 16 h in toluene, filtered and the filtrate was concentrated *in vacuo* to afford the phthalide in greater than 95% purity as determined by  $^1\text{H}$  NMR spectroscopy.

### Acknowledgement

This work was supported financially by the National Institutes of Health (GM-56164), The Skaggs Institute for Chemical Biology and The Scripps Research Institute. We thank BASF AG for the gift of polytetrahydrofuran 250.

### References and Notes

- (1) Snieckus, V. *Chem. Rev.* **1990**, *20*, 879.
- (2) Brown, R. C. D. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3293.
- (3) Havez, S.; Begtrup, M.; Vedso, P.; Anderson, K.; Ruhland, T. *J. Org. Chem.* **1998**, *63*, 7418.
- (4) Fyles, T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 935.
- (5) Farrall, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877.
- (6) Boehm, T. L.; Showalter, H. D. H. *J. Org. Chem.* **1996**, *61*, 6498.
- (7) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* In press.
- (8) Mitchell, A. R.; Kent, S. B. H.; Engelhard, M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845.
- (9) Charreyre, M.-T.; Razafindrakoto, V.; Veron, L.; Delair, T.; Pichot, C. *Macromol. Chem. Phys.* **1994**, *195*, 2141.
- (10) Wilson, M. E.; Paech, K.; Zhou, W.-J.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 5094.
- (11) Hori, M.; Gravert, D. J.; Wentworth Jr., P.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2363.
- (12) Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595.

Article Identifier:

1437-2096,E;1999,0,09,1438,1440,ftx,en;S03799ST.pdf