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# Resin-to-resin Petasis borono-Mannich reaction between dialkylamino resins and supported boronic acids

**Kim A. Thompson and Dennis G. Hall***

*Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2. E-mail: dennis.hall@ualberta.ca; Fax: (+1) (780) 492-8231; Phone: (+1) (780) 492-3141*

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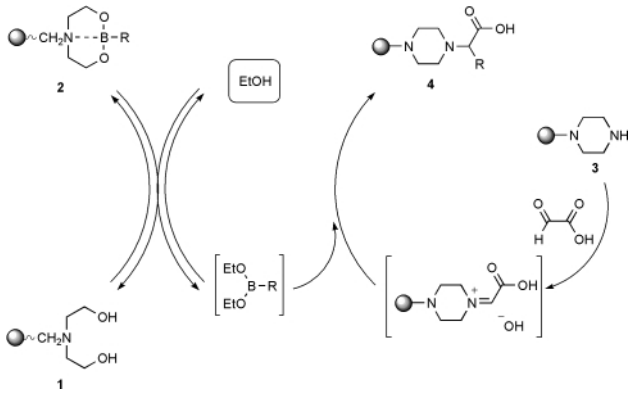
**Iminium intermediates, formed from the condensation of glyoxylic acid and resins functionalized with a secondary amine, are coupled to boronic acids transferred to solution from the corresponding [*N*,*N*-diethanolaminomethyl polystyryl boronates by *in situ* transesterification with the ethanol co-solvent to provide arylglycine derivatives.**

In comparison with the traditional approach to solid-phase synthesis where a single resin-bound substrate is employed, the simultaneous use of two or more heterogeneous substrates, reagents or catalysts has seldom found real synthetic utility. Resin-to-resin transfer reactions (RRTR) constitute one type of multiresin system whose particular advantage is to allow the practice of solid-phase synthesis in a convergent fashion.[1] In RRTR, one resin-bound substrate is transferred to solution-phase by action of a phase-transfer agent, or chaperone, and coupled *in situ* to another resin-bound substrate. The concept of RRTR could find applications in combinatorial chemistry where each resin-bound substrate can be a member of a respective library assembled using the practical techniques of solid-phase synthesis. Recently, we have reported a successful RRTR system to effect Suzuki cross-coupling reactions between resin-bound aryl iodides and arylboronic acids supported onto [*N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS).[2] The DEAM-PS resin facilitates the synthesis of functionalized arylboronic acids which can otherwise be difficult to isolate and handle in solution.[3] Their subsequent use in RRTR processes eliminates time-consuming cleavage and transfer operations, thereby considerably simplifying the outlook of library synthesis by manual or automated means. Herein, we describe the preliminary optimization of a resin-to-resin borono-Mannich reaction that produces arylglycine derivatives. Compounds of this nature are of particular interest for their biological activity.[4]

The boronic acid Mannich reaction first reported by Petasis[5] is compatible with a wide range of solvents including hydroxylic ones.[5–8] We envisioned that an alcohol, employed as co-solvent, could act as a neutral phase transfer agent required to cleave the DEAM-PS supported boronic acids under mild conditions appropriate toward a RRTR system. The boronic acid liberated *in situ* as an ester could then add to the imine formed between an amino functionalized resin and an activated aldehyde such as glyoxylic acid (Scheme 1).[6] We have first optimized conditions using DEAM-PS supported *p*-tolylboronic acid (**2**, R = 4-Me-$C_6H_4$- in Scheme 1), piperazinyltrityl resin, and glyoxylic acid in a semi-automated synthesizer.† The reaction was found to be rather slow and strongly dependent on the nature of the solvent system, THF–EtOH (7:1) and DMF–*n*-BuOH (7:1) being first and second best respectively. The current set of optimal experimental conditions first involve incubating the dialkylamino resin with glyoxylic acid monohydrate (1.1 eq.) for 2 h in dry THF at rt.‡ Then, four eq. of DEAM-PS bound boronic acid are added along with the appropriate volume of 8:3 THF–EtOH. The suspension is shaken at 65 °C for up to 48 h. This way, conversion levels superior to 75% were observed in the case of *p*-tolylboronic acid as seen after cleavage of the final resin mixture **1** and **4** with 5% trifluoroacetic acid/DCM to give the corresponding amino acid product **5a** as a bis(trifluoroacetate) salt (Table 1, entry 1).§ The rest of unreacted starting resin **3** is cleaved into the bis(trifluoroacetate) salt of piperazine (**6**) which can be eventually removed by precipitation. There are no other by-products observed, as the left over DEAM-PS resin (**1**) does not give any artifacts upon treatment with trifluoroacetic acid in the product release step. Interestingly, the transesterification of resin **2** with EtOH, a process required for phase transfer of the DEAM-PS-boronate, appears to be a dynamic equilibrium. The latter is driven forward by the large excess of EtOH, and through consumption of the boronic acid which adds to the putative iminium intermediate to form supported product **4** (Scheme 1). We have devised control experiments aimed at measuring the extent of transesterification of DEAM-PS supported *p*-tolylboronic acid in 7:1 THF–EtOH. Equilibrium is reached within 15 min of exposure of **2** to the 7:1 THF–EtOH solvent. Successive incubations of the resin under constant resin–solvent proportions, followed by rinses with dry THF, revealed that approximately 40% *p*-tolylboronic acid is released from the resin under these conditions.¶ In fact, since there is some left over DEAM-PS-boronate (**2**) at the end because of the transesterification equilibrium, we have found it necessary to include water–THF washes in order to wash off all excess boronic acid from the resin mixture prior to the acidolytic release of product **5**.‖ It is noteworthy to mention that although this RRTR was found to proceed in the absence of ethanol (the water introduced from the aldehyde hydrate may be sufficient to promote phase transfer of the boronic acid) conversion levels were generally higher in THF–EtOH.

Next we have studied substrate generality for this new RRTR system (Scheme 2). As shown in Table 1, conversion values and product yields were generally good except for the RRTR of electron-poor arylboronic acids.§ Thus, conversion values were highest for DEAM-PS supported *p*-methoxybenzeneboronic acid (entries 3, 7, 8), and lowest for *p*-bromophenylboronic acid (entry 4). According to entry 6, DEAM-PS-supported alkenylboronic acids are also appropriate substrates. In this case the use




**Scheme 1** Borono-Mannich resin-to-resin transfer reaction between boronic acids supported onto [*N*,*N*-diethanolaminomethyl polystyrene (**2**) and the iminium intermediate formed from a dialkylamino resin (**3**) and glyoxylic acid.



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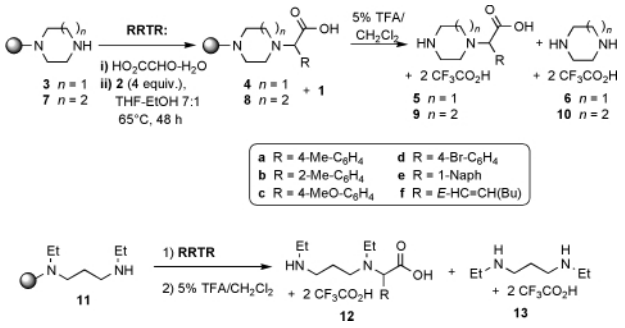


**Scheme 2** RRTR of **3**, **7**, **11** with different DEAM-PS-boronates and cleavage of the final resin mixture to provide arylglycine derivatives **5**, **9**, and **12**.

**Table 1** Preparation of arylglycine derivatives by borono-Mannich RRTR[a]

| Entry | Amino resin | HEAM-PS-boronate **2** | Product | Conversion (%)[b] | Yield[c] |
|---|---|---|---|---|---|
| 1 | **3** | R = 4-Me-$C_6H_4$ | **5a** | 79 | 85 |
| 2 | **3** | R = 2-Me-$C_6H_4$ | **5b** | 81 | 73 |
| 3 | **3** | R = 4-MeO-$C_6H_4$ | **5c** | 90 | > 95 |
| 4 | **3** | R = 4-Br-$C_6H_4$ | **5d** | 21 | 10 |
| 5 | **3** | R = 1-Naph | **5e** | 85 | 90 |
| 6 | **3** | R = *E*-HC=CH(Bu) | **5f** | 89 | > 95 |
| 7 | **7** | R = 4-MeO-$C_6H_4$ | **9c** | 95 | 91 |
| 8 | **11** | R = 4-MeO-$C_6H_4$ | **12c** | 76 | 82 |

[a] Preparation of resin substrates, RRTR trials, and subsequent cleavage of the resin mixture were carried out as indicated in the Notes and references section.†,‡ [b] Based on the relative amounts of product and respective bis(trifluoroacetate) salt **6**, **10**, or **13** calculated by integration of relevant peaks by $^1$H NMR after 24–48 h reaction time. [c] Yields of crude product based on $^1$H NMR analysis with an internal standard.

of a RRTR strategy using DEAM-PS resin is even more advantageous for handling and storage purposes since the otherwise air-sensitive alkenylboronic acids can be stabilized through immobilization as diethanolamine** adducts. An example using an acyclic amine (**11**) was equally successful (entry 8), showing that in principle a variety of secondary amines such as terminal *N*-alkylamino acids could be employed. Although only electron-rich arylboronic acids currently provide satisfactory conversions to crude material of high purity, analytically pure samples of most reported compounds can be obtained following precipitation with MeOH–ether, and filtration of the unreacted dialkylamine as a bis(trifluoroacetate) diammonium salt. We have also confirmed that the examples performed in a RRTR format provide yields comparable to reactions using non-supported boronic acids.

By minimizing cleavage, solvent concentration, and transfer operations this new borono-Mannich RRTR is thus potentially useful in the convergent solid-phase synthesis of libraries of arylglycine derivatives. In principle, this could be achieved by combining libraries of dialkylamino resins with libraries of DEAM-PS-supported arylboronic acids made by solid-phase derivatization of functionalized ones.[2,3] Studies such as this one looking at the structural and electronic preferences of substrates are crucial in order to select the most appropriate types of building blocks.

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## Notes and references

† *Materials and methods*: *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS) was made according to ref. 3. All boronic acids were purchased from commercial sources (Aldrich, Lancaster, or CombiBlocks) and were loaded onto DEAM-PS as described in ref. 3. The dialkylaminotrityl resins were made by the condensation of excess diamine (20 equiv.) onto commercial chlorotrityl polystyrene (Rapp Polymere) swelled in NMP. Loading measurements were carried out by analysis of nitrogen content. For RRTR's, runs were done in 10 mL Teflon fritted vessels on a Quest 210 instrument with solvent wash unit (Argonaut Technologies). Cleavage was effected on-line and crude products were obtained after evaporation of solvents. Yields and purity were estimated by comparison with an internal NMR standard (EtOAc, 15 s relaxation delay).

‡ *Typical procedure for the borono-Mannich RRTR. Preparation of* **5c**. To piperazinyltrityl resin **3** (32 mg, 0.030 mmol, theor. loading: 0.95 mmol $g^{-1}$) weighed out in a reaction vessel was added a solution of glyoxylic acid monohydrate (0.032 mmol) in dry THF (2 mL). The suspension was allowed to mix at rt under a nitrogen atmosphere for 2 h. An excess of DEAM-PS boronic ester **2c** (127 mg, 0.120 mmol, theor. loading: 0.95 mmol $g^{-1}$) was then added followed by 1.5 ml of 8:3 THF–EtOH. The suspension was mixed at 65 °C for 48 h under a nitrogen atmosphere and then cooled to rt. The resin mixture was filtered and rinsed with 8 : 3 THF–EtOH (3×), 2 : 1 THF–$H_2O$ (3×) and $CH_2Cl_2$ (5×), mixed with 3 ml of 5% TFA/$CH_2Cl_2$ in the same vessel at rt for 1 h, then filtered and rinsed with $CH_2Cl_2$ (3×) and MeOH (2×). The combined filtrates were concentrated and dried under high vacuum for 12 h to afford crude **5c** as a clear oil (14 mg, 90% conversion). An analytically pure sample was obtained by dissolving the oil in a small amount of MeOH followed by addition of ether, filtration of the precipitate, and concentration of the resulting solution.

§ *Selected data for all products*: **5a**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.30 (d, $J$ = 8.0 Hz, 2H), 7.20 (d, $J$ = 8 Hz, 2H), 4.17 (s, 1H), 3.23–3.20 (m, 4H), 2.77–2.74 (m, 4H), 2.33 (s, 3H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 173.5, 140.5, 132.0, 130.7, 130.1, 73.3, 48.1, 44.3, 21.2; ESMS 235.1 (M + H$^+$). **5b**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.40 (d, $J$ = 6.0 Hz, 1H), 7.24–7.18 (m, 3H), 4.50 (s, 1H), 3.20–3.16 (m, 4H), 2.85–2.82 (m, 4H), 2.45 (s, 3H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 174.2, 138.9, 134.7, 131.8, 129.3, 129.1, 127.1, 69.3, 47.7, 44.9, 19.4; ESMS 235.3 (M + H$^+$). **5c**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.34 (d, $J$ = 8.6 Hz, 2H), 6.93 (d, $J$ = 8.9 Hz, 2H), 4.13 (s, 1H), 3.79 (s, 3H), 3.23–3.19 (m, 4H), 2.75–2.72 (m, 4H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 174.3, 161.7, 131.2, 127.9, 115.2, 73.1, 55.7, 48.3, 44.7; ESMS 251.1 (M + H$^+$). **5d**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.55 (d, $J$ = 8.5 Hz, 2H), 7.36 (d, $J$ = 8.5 Hz, 2H), 4.22 (s, 1H), 3.25–3.19 (m, 4H), 2.77–2.73 (m, 4H); ESMS 301.1 (M + H$^+$). **5e**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 8.43 (d, $J$ = 7.9 Hz, 1H) 7.91–7.88 (m, 2H), 7.60–7.45 (m, 4H), 5.06 (s, 1H) 3.16–3.12 (m, 4H), 2.93–2.90 (m, 4H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 174.3, 135.7, 133.4, 132.4, 130.5, 129.8, 128.4, 127.6, 127.1, 126.2, 125.2, 70.1, 47.9, 45.2; ESMS 271.1 (M + H$^+$). **5f**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 5.89 (dt, $J_1$ = 15.0 Hz, $J_2$ = 7.0 Hz, 1H) 5.48 (dd, $J_1$ = 15.0 Hz, $J_2$ = 8.0 Hz, 1H) 3.70 (d, $J$ = 8.0 Hz, 1H) 3.26–3.23 (m, 4H), 2.95–2.87 (m, 2H), 2.84–2.76 (m, 2H), 2.12 (app. q, $J$ = 7.0 Hz, 2H) 1.44–1.29 (m, 4H) 0.92 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 173.9, 140.5, 124.3, 71.8, 48.1, 44.6, 33.2, 32.2, 23.2, 14.2; ESMS 227.2 (M + H$^+$). **9c**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.38 (d, $J$ = 8.7 Hz, 2H), 6.96 (d, $J$ = 8.6 Hz, 2H), 4.65 (s, 1H), 3.80 (s, 3H), 3.34–3.21 (m, 2H) 3.21–3.10 (m, 4H), 3.01–2.97 (m, 2H), 2.07–2.04 (m, 2H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 174.4, 161.8, 131.5, 128.0, 115.4, 73.1, 55.8, 53.3, 49.2, 46.7, 45.9, 26.1; ESMS 265.1 (*M* + H$^+$). **12c**: $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 7.48 (d, $J$ = 8.8 Hz, 2H), 7.03 (d, $J$ = 8.8 Hz, 2H), 4.96 (s, 1H), 3.83 (s, 3H), 3.13–3.01 (m, 8H), 2.18–2.03 (m, 2H), 1.33–1.25 (m, 3H); ESMS 295.4 (M + H$^+$).

¶ The reverse reaction (**1** + *p*-tolylboronic acid) gives a similar outcome under the same conditions, showing that the transesterification process is under equilibrium.

‖ The DEAM-PS boronate linkage is very sensitive to water even in trace amounts. In contrast with alcoholysis, hydrolysis appears to be irreversible and quantitative.

** The IUPAC name for diethanolamine is 2,2′-iminodiethanol, and for DEAM-PS is [*N*,*N*-bis(2-hydroxyethyl)amino]methyl polystyrene.

1 For a recent example, see: Y. Hamuro, M. A. Scialdone and W. F. DeGrado, *J. Am. Chem. Soc.*, 1999, **121**, 1636; and references cited therein.
2 M. Gravel, C. Bérubé and D. G. Hall, *J. Comb. Chem.*, 2000, **2**, 228.
3 D. G. Hall, J. Tailor and M. Gravel, *Angew. Chem., Int. Ed.*, 1999, **38**, 3064.
4 For example, see: J. S. Bedingfield, M. C. Kemp, D. E. Jane, H. W. Tse, P. J. Roberts and J. Watkins, *J. Pharmacol.*, 1995, **116**, 3323.
5 N. A. Petasis and I. Akritopoulou, *Tetrahedron Lett.*, 1993, **34**, 583.
6 N. A. Petasis and I. A. Zavialov, *J. Am. Chem. Soc.*, 1998, **120**, 11 798.
7 T. K. Hansen, N. Schlienger, B. S. Hansen, P. H. Andersen and M. R. Bryce, *Tetrahedron Lett.*, 1999, **40**, 3651.
8 (*a*) S. R. Klopfenstein, J. J. Chen, A. Golebiowski, M. Li, S. X. Peng and X. Shao, *Tetrahedron Lett.*, 2000, **41**, 4835; (*b*) A. Golebiowski, S. R. Klopfenstein, J. J. Chen and X. Shao, *Tetrahedron Lett.*, 2000, **41**, 4841.