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Hydantoin formation by *cyclo*-elimination: reactivity difference between Merrifield- and Wang-derived resins

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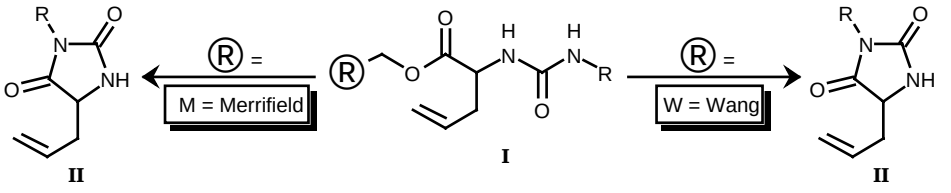
Abstract

cyclo-Elimination reactivity differences in **I**→**II** are reported. These reactivity differences dictate the selection of Wang resin for *N*1-substituted hydantoin formation and Merrifield resin for *N*1-unsubstituted hydantoin formation.

Successful solid-phase chemistry requires careful selection of (i) the solid-support which must be compatible with the synthetic transformations, (ii) the linker technology which must accommodate the chemistry and yet liberate the final product with high efficiency, (iii) the protecting group strategies employed which must be coordinated with target functionality and reactivity, and (iv) the solvents employed which must effectively support both the chemistry and the resin.[1] Numerous studies have established that linkers which incorporate *cyclo*-elimination[2] release strategies are particularly important in solid-phase organic synthesis in that only cyclizable precursors are positioned for release, hence contributing to final product purity. Since DeWitt et al.[3] first reported production of an hydantoin library from Wang resin using an ester linker with *cyclo*-elimination release, a number of related strategies for hydantoin production have been reported. Of these, some protocols[4] have employed Wang-based ester linkers ($\mathbf{I}^{®=W}$; ® = Wang), while others[5] have employed Merrifield-based ($\mathbf{I}^{®=M}$; ® = Merrifield) ester linkers. Given the widespread use of these two resins, it is surprising that there are no reports regarding *cyclo*-elimination differences in these two ester-linked resins. We report here the discovery of fundamental reactivity idiosyncrasies between these resins in $\mathbf{I}^{®=M/W}$→**II**; these reactivity differences dramatically bias resin selection for library production.



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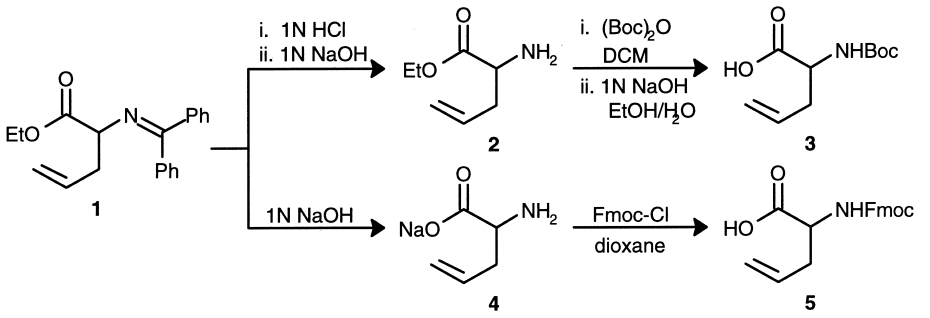
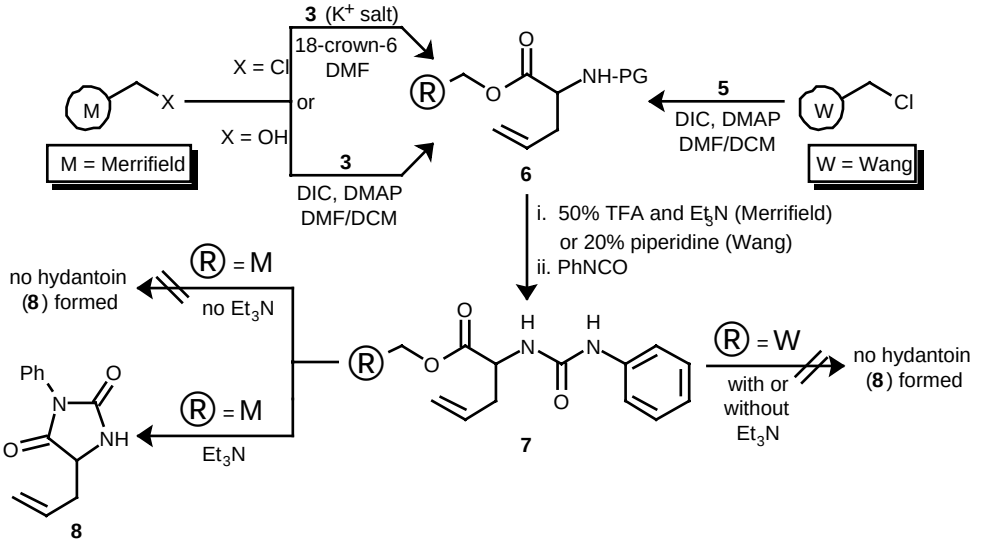
To compare the reactivity differences, allyl substituted *N*-protected amino ester **1**[6] (3 g, 9.8 mmol scale; Scheme 1), an important precursor for the construction of hydantoin–isoxazoline heterocycles, was hydrolyzed and subsequently Boc- or Fmoc-protected to afford **3** (72% overall yield) or **5** (78% overall yield), respectively. This difference in *N*-protection reflects Boc-compatibility with Merrifield resin and Fmoc-compatibility with Wang resin.



Scheme 1.

These protected amino acids were coupled with Merrifield (either DIC-mediated coupling of **3** or 18-crown-6-mediated coupling of the potassium salt of **3**) and Wang (DIC-mediated coupling of **5**; Scheme 2) resin. After removal of the Boc or Fmoc protecting group, each amino ester bound resin was treated with phenyl isocyanate to give urea $\mathbf{7}^{\circledR=M/W}$ (urea FTIR at 1656 cm^{-1}) and the cyclization to the final hydantoin was investigated. Without base, neither of these resins released hydantoin **8**. However, treating THF-swollen Merrifield resin $\mathbf{7}^{\circledR=M}$ with Et_3N at gentle reflux (60°C, overnight) delivered **8** in 95% overall yield. Identical conditions with Wang resin $\mathbf{7}^{\circledR=W}$ gave no trace of **8**.

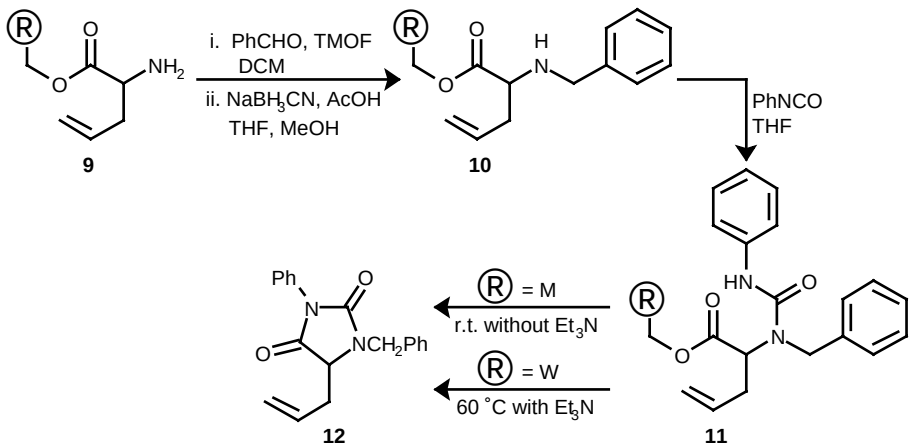


Scheme 2.

Protocol for $\mathbf{7}^{\circledR=M}\rightarrow\mathbf{8}$: acid **3** (0.79 g, 3.68 mmol) and DIC (0.46 g, 3.68 mmol) were dissolved in DMF/CH_2Cl_2 (2 mL/8 mL) and this solution was added to a flask containing hydroxy-

methylene polystyrene resin (1.35 g, 0.92 mmol, 0.68 mmol/g). A solution of DMAP (45 mg, 0.37 mmol) in DMF/CH_2Cl_2 (2 mL/8 mL) was added and the reaction mixture was stirred overnight at ambient temperature. The resin was washed with DMF, CH_2Cl_2, and ether, and dried to give $\mathbf{6}^{®=M}$ (=Merrifield resin; PG=Boc). This resin was treated with 50% TFA in DCM (10 mL) at rt for 1 h at which time the resin was washed with DMF, DCM, and 20% Et_3N in DCM (10 mL×5). The resulting DCM-swollen resin was treated with phenyl isocyanate (0.44 g, 3.68 mmol) at rt for 10 h, washed with DMF, THF, and DCM, and dried to afford Merrifield-derived resin $\mathbf{7}^{®=M}$. This resin was treated with Et_3N (0.37 g, 3.68 mmol) in THF (10 mL) at 60°C overnight. The combined solution from resin filtration and washing (THF) was concentrated under reduced pressure and purified by a short silica-gel column to afford hydantoin **8** (0.19 g, 0.87 mmol, 95% from Merrifield resin) as a solid.[7]

As outlined in Scheme 3, we next investigated hydantoin formation from polymer-bound *N*1-substituted urea $\mathbf{11}^{®=M/W}$. This *N*1-substituent was introduced by reductive *N*-alkylation of amino resin $\mathbf{9}^{®=M/W}$ using, for example, benzaldehyde to afford resin $\mathbf{10}^{®=M/W}$. Subsequent urea formation gave $\mathbf{11}^{®=M/W}$. The targeted hydantoin **12** was released from Merrifield resin (92% overall yield) even at rt without base (Scheme 3). In contrast, Wang resin shows no release of hydantoin after 4 days at rt. Release of **12** from Wang resin requires either prolonged heating (refluxing THF, 3 days) or addition of base (Et_3N). We attribute the facile *cyclo*-elimination of **12** from $\mathbf{11}^{®=M}$ (compared with $\mathbf{7}^{®=M}\rightarrow\mathbf{8}$ which requires Et_3N/THF/reflux) to a strong buttressing effect in **11**.[8] Comparing release results from $\mathbf{11}^{®=M}$ and $\mathbf{11}^{®=W}$ suggests that the Wang *p*-benzyloxy substituent produces an electron-donating effect on the ester carbonyl carbon of the linker, which results in significant deactivation of the system to *cyclo*-elimination. By way of contrast, it is noteworthy that the thiourea® analogues of $\mathbf{7}^{®=M/W}$ and $\mathbf{11}^{®=M/W}$ undergo *cyclo*-elimination to deliver the thiohydantoin analogues of **8** and **12** without requiring addition of base.[9]



Scheme 3.

Protocol for $\mathbf{11}^{®=M}\rightarrow\mathbf{12}$: resin $\mathbf{9}^{®=M}$ (from 1 g of Merrifield resin, 0.68 mmol/g) was treated with benzaldehyde (0.43 g, 4.08 mmol) in TMOF/THF (5 mL/5 mL) for 4 h at ambient temperature, then washed with TMOF/THF (1:1). Subsequent addition of $NaCNBH_3$ (85 mg, 1.36 mmol) in THF/MeOH/AcOH (9 mL/1 mL/0.1 mL) and agitating overnight at ambient temperature, followed by washes with MeOH/THF (1:3), MeOH/DMF (1:3), DMF, and

CH_2Cl_2, and gave Merrifield-derived resin $\mathbf{10}^{®=M}$, which was dried under nitrogen. Merrifield-derived resin $\mathbf{10}^{®=M}$ was treated with phenyl isocyanate (0.32 g, 2.72 mmol) in THF (10 mL) at 60°C overnight to sequentially effect urea formation (giving $\mathbf{11}^{®=M}$) and *cyclo*-elimination to produce hydantoin **12**. The resin was washed with THF and the combined organic solvent was evaporated under reduced pressure. The resulting residue was purified by short-pass column chromatography (20% ethyl acetate in hexane) to give **12** (0.191 g, 0.63 mmol, 92%).[10]

Protocol for $\mathbf{11}^{®=W}\rightarrow\mathbf{12}$: acid **5** (3 g, 8.89 mmol) and Wang resin (1.73 g, 2.22 mmol, 1.28 mmol/g) were coupled using DIC (1.12 g, 8.89 mmol) and DMAP (0.11 g, 0.89 mmol) following the same procedure as above. The resultant resin **6** (PG = Fmoc) was treated with 20% piperidine at ambient temperature for 1 h, washed with DMF and DCM, and dried to give Wang-derived resin $\mathbf{9}^{®=W}$. Reductive amination following the same procedure as for making Merrifield-derived resin $\mathbf{10}^{®=M}$ afforded Wang-derived resin $\mathbf{10}^{®=W}$. This resin was treated with phenyl isocyanate (1 g, 8.89 mmol) in THF (10 mL) at rt for 10 h, washed with DMF, THF, and DCM, and dried to afford the urea bound Wang-derived resin $\mathbf{11}^{®=W}$. Treatment of this resin with Et_3N (0.9 g, 8.89 mmol) in THF (20 mL) at 60°C overnight, washes of the resin with THF, and concentration of the combined filtrate afforded hydantoin **12** (0.638 g, 2.28 mmol, 94%) as a liquid.

These reactivity differences dictate the selection of Wang resin for library production targeting *N*1-substituted hydantoins since Merrifield-derived resin suffers premature *cyclo*-elimination of the final hydantoin product during filtration and resin washing. Merrifield resin can be effectively employed in the production of *N*1-unsubstituted hydantoins.

Acknowledgements

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6. See reference 5d.
7. **8**: FTIR (KBr) 1778, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44–7.35 (m, 5H), 6.96 (s, 1H), 5.81–5.72 (m, 1H), 5.25–5.19 (m, 2H), 4.18 (t, 2H, $J = 5.5$ Hz), 2.71–2.65 (m, 2H), 2.56–2.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 156.8, 131.3, 130.8, 129.0, 128.2, 126.1, 120.3, 56.4, 35.9.
8. Park, K.-H.; Kurth, M. J. *Tetrahedron Lett*. **1999**, *40*, 5841.

9. Thiodantoin analogues of **8** and **12** were prepared following the procedure described above except using phenyl isothiocyanate. The thiourea analogues bound resin of **7** an **11** were not isolated. Thiohydantoin analogue **8** (94% from Merrifield resin, 92% from Wang resin): FTIR (thin film) 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.54–7.51 (m, 3H), 7.48–7.28 (m, 2H), 5.82–5.79 (m, 1H), 5.32–5.26 (m, 2H), 4.33 (dd, 1H, $J=7.57$, 4.24 Hz), 2.82–2.75 (m, 1H), 2.61–2.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.8, 172.8, 132.5, 130.5, 129.3, 129.2, 128.2, 120.9, 59.2, 35.6. Thiohydantoin analogue **12** (90% from Merrifield resin, 93% from Wang resin): FTIR (thin film) 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.23 (m, 10H), 5.87 (d, 1H, $J=15.0$ Hz), 5.70–5.60 (m, 1H), 5.27–5.22 (m, 2H), 4.42 (d, 1H, $J=15.0$ Hz), 4.11 (t, 1H, $J=4.2$ Hz), 2.74 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 172.2, 134.7, 133.4, 129.3, 129.1, 129.0, 128.4, 128.3, 121.1, 60.7, 48.5, 33.1.
10. **12**: FTIR (thin film) 1773, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.11 (m, 10H), 5.66–5.61 (m, 1H), 5.24–5.18 (m, 2H), 5.13 (d, 1H, $J=15.3$ Hz), 4.17 (d, 1H, $J=15.3$ Hz), 4.00 (t, 1H, $J=4.2$ Hz), 2.70–2.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 155.5, 135.4, 131.7, 130.0, 129.0, 128.9, 128.3, 128.2, 128.1, 126.0, 120.7, 58.1, 44.9, 32.9.