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A thermally-cleavable linker for solid-phase synthesis

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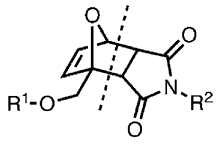
Abstract—Oxabicyclo[2.2.1]norbornenes constitute a convenient and readily cleaved linker for solid-phase organic synthesis. A simple and inexpensive furfuryl-substituted resin has been shown to capture and release maleimide dienophiles under conditions compatible with intermediate synthetic steps. The synthesis of β-amino, -thiophenoxy, and -hydrazino alcohols by epoxide ring opening, and maleimide-functionalized Leu-enkephalin by standard peptide coupling techniques, are described to illustrate the utility of the solid-phase synthesis methodology.

The utility of solid-phase organic synthetic methods depends upon the ease with which tethered products can be removed from the solid support. The development of cleavable linkers for this purpose has been the subject of much effort, and a wide variety of systems exist to accommodate various reaction conditions.[1] Cleavage is most commonly accomplished by treatment with acid; other methods include the use of base, fluoride, oxidants, olefin metathesis, and irradiation. We report here the development of a simple linker that is cleaved by thermal promotion of retro-Diels–Alder (rDA) reactions,[2] and a demonstration of its use in solid-phase organic synthesis.

Furan Diels–Alder (DA) adducts have found extensive use in organic synthesis;[3] the resulting 7-oxanorbornene is often elaborated and/or ring opened, providing routes to a wealth of valuable synthetic targets. The relative ease of formation and rDA cleavage of these systems provides the basis for a set of linkers of varying thermal stability for use in solid-phase organic synthesis. One previous report has appeared on this topic,[4] and other thermally-cleaved linkers have also been developed.[5] In addition, the Diels–Alder reaction of a resin-bound maleimide has been used as a scavenger for anthracene-tagged molecules with subsequent release by ester hydrolysis,[6] furan-substituted resins have been used to capture and release C_{60},[7] and [4+2] cycloaddition and cycloreversion processes have been used to modulate the properties of a polymer.[8] We describe here the properties of the linkage based on adduct **1**, which incorporates a maleimide dienophile in its construction. This system is particularly appropriate for the attachment of amine-containing molecules to solid supports, succinimides, and phthalimides being widely used as amine protecting groups.[9]



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To demonstrate the utility of maleimide–furan linker **1**, epoxide-functionalized maleimides **5a** and **5b** were prepared as shown in Scheme 1. *N*-(methoxycarbonyl)maleimide **2** (formed from maleimide and methyl chloroformate)[10] was a convenient starting material, undergoing smooth exchange with amino alcohols to give **3**. The maleimide group was protected for further manipulations as the *exo* furan DA adduct **4**. Attachment of an enantiomerically pure glycidyl fragment[11] was then accomplished in good yield, followed by deprotection by rDA reaction to provide **5**. The furan-substituted polystyrene resin **6** was prepared on 25 g scale from furfuryl alcohol and standard Merrifield resin under basic conditions (NaH, KI, *N*,*N*-dimethylacetamide solvent, 25 °C) and is therefore inexpensive and easily accessed.

Keywords: Solid-phase; Linker; Cleavage; Peptides.
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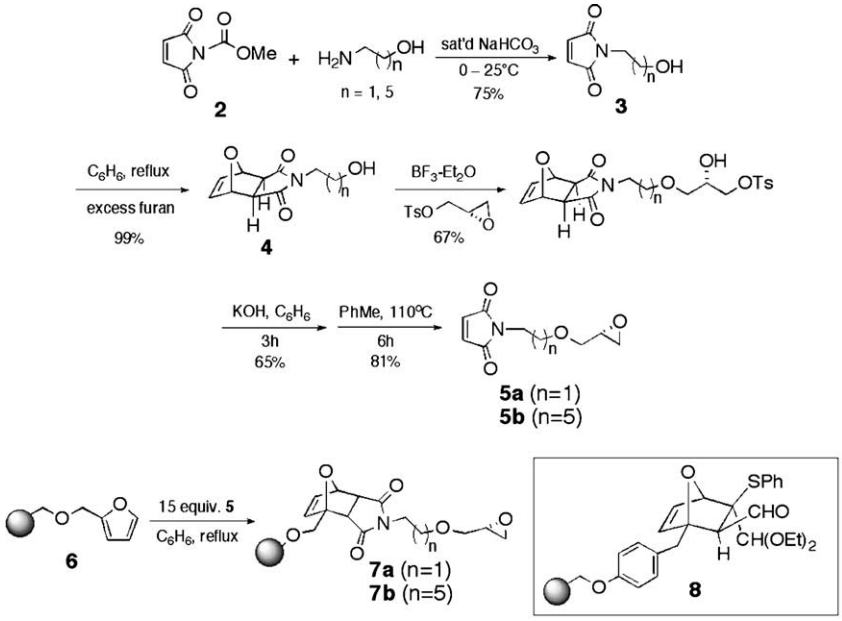


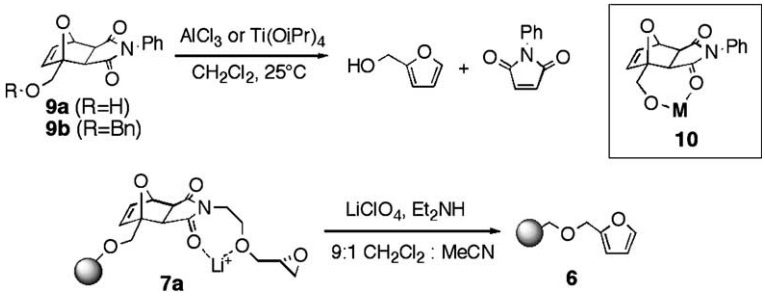
Scheme 1.

Attachment of maleimides such as **5** is accomplished by heating an excess of the dienophile with the resin in refluxing benzene. While a safety-catch scheme has been described in which the Diels–Alder adduct is modified to give **8** and then cleaved at low temperature,[4] we have found it convenient to rely upon mass action to load the resin and simple heating to remove the group when desired. The process may be conveniently monitored by IR spectroscopy to detect the attached imide group ($\nu_{C=O} = 1770\ cm^{-1}$). The density of functional groups on the resin can be diluted by mixing **5** with an unfunctionalized dienophile such as *N*-methylmaleimide (NMM) in the desired ratio, since we find that **5** and NMM react at equal rates. This allows for precise control of resin loading from a single starting chloromethylated polymer.

A preliminary investigation of the stability of such DA adducts was performed using compound **4**, which was found to have a half-life toward cycloreversion of approximately 36 h at 80 °C. This provides ample opportunity to perform chemistry on the attached groups without cleavage from the solid-phase. Partial cleavage for analytical purposes is easily accomplished by heating for a few hours, leaving most of the resin-bound compound unchanged for solid-phase use. Cleavage of **7a** and **7b** in refluxing toluene (110 °C) required 6 h to reach completion, with compounds **5a** and **5b** being isolated directly in pure form without chromatography.

We have found maleimide adducts of furfuryl alcohol to be sensitive to Lewis acids; thus, compound **9a** was cleaved at room temperature in the presence of $AlCl_3$ or $Ti(O^iPr)_4$, whereas benzyl ether **9b** was stable to these conditions (Scheme 2). The chelating interaction in **10** is presumed to be responsible for activating the carbonyl group for rDA reaction. Similarly, the attempted ring opening of resin-bound epoxide **7a** with diethylamine in the presence of lithium perchlorate[12] gave rise to rDA reaction faster than epoxide ring opening, again presumably because of a chelating interaction with the Lewis acidic metal as shown. The chain-extended analogue **7b** (Scheme 1) does not undergo rDA cleavage under these conditions and is also stable to 5 M $LiClO_4$ in diethyl ether, which has been demonstrated to catalyze the cycloreversion of some furan cycloadducts.[13]

Nucleophilic ring opening of resin-bound epoxide **7b** provided convenient access to a series of enantiomeri-



Scheme 2.

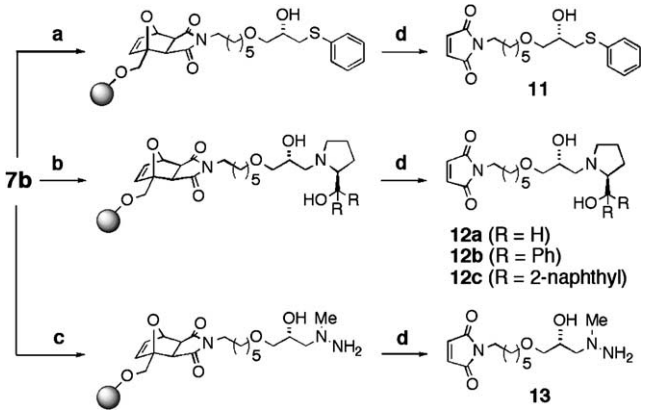


Figure 1. Synthesis of chiral alcohol maleimides. Reagents and conditions: (a) PhSH, K_2CO_3, acetone, 25 °C; (b) amine, $LiClO_4$ or $Mg(ClO_4)_2$, 9:1 CH_2Cl_2–MeCN, 25 °C; (c) $MeNHNH_2$, $LiClO_4$, 9:1 CH_2Cl_2–MeCN, 25 °C; (d) toluene, 110 °C, 8 h.

cally pure compounds, as shown in Figure 1.[14] The tertiary amino alcohols **12** are useful as chiral catalysts of dialkylzinc addition to carbonyl compounds. In all cases, the removal of functionalized maleimides from the polystyrene support was accomplished by heating the resin to reflux in toluene for 8 h. Infrared spectra of the recovered polymer showed no sign of the imide carbonyls after this treatment, and the resultant polymer **6** could be recycled without difficulty. The released compounds **11**–**13** were isolated in >70% yield without the need for further purification.

Resin **6** was also employed in solid-phase peptide synthesis; for demonstration purposes, the neuropeptide Leu-enkephalin (YGGFL),[15] was chosen. The amino-terminated adduct **14** was generated and standard Fmoc steps were used to install the proper residues (Fig. 2). Thermal cleavage gave the appropriate maleimide-

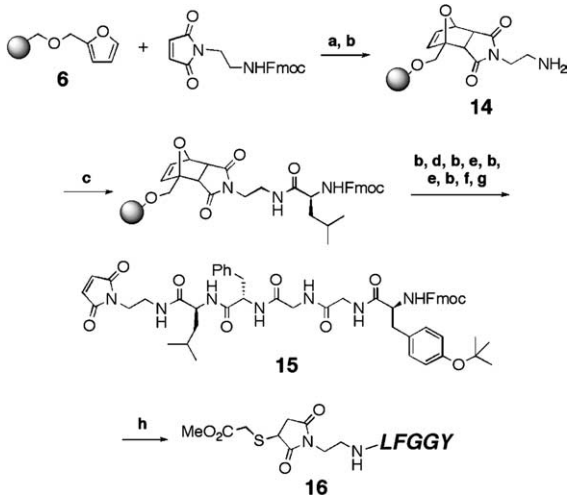
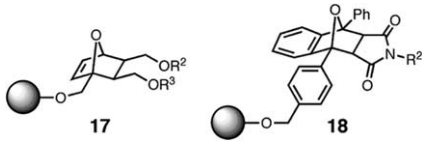


Figure 2. Synthesis and thiol attachment of Leu-enkephalin. Reagents and conditions: (a) benzene, 80 °C; (b) 20% piperidine, DMF; (c) Fmoc-L-Leu, HBTU, $EtN(i\text{-}Pr)_2$, DMF; (d) Fmoc-L-Phe, HBTU, $EtN(i\text{-}Pr)_2$, DMF; (e) Fmoc-L-Gly, HBTU, $EtN(i\text{-}Pr)_2$, DMF; (f) Fmoc-L-Tyr-O-*t*-Bu, HBTU, $EtN(i\text{-}Pr)_2$, DMF; (g) toluene, reflux, 12 h; (h) $HSCH_2CO_2Me$, $EtN(i\text{-}Pr)_2$.

tagged pentapeptide **15**. While not traceless, this methodology is attractive if one wishes to attach the compounds produced to a biological target by means of ligation to a thiol residue. Accordingly, methylthioacetate was used to trap the released maleimide to give **16**; HPLC analysis showed the material to be >85% pure.

We have shown here that the simple furfuryl-substituted resin **6** can capture and release dienophiles such as maleimides to facilitate the synthetic elaboration of these useful compounds. The relatively mild conditions necessary for cleavage have also prompted us to develop two other linkers (**17** and **18**), which are cleaved at higher temperatures (≥150 °C). Their construction and application will be described separately.



Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.12.067.

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14. *Preparation of resin* **7b**: resin **6** (50 mg, 0.64 mequiv/g) and maleimide **5b** (100 mg, 0.4 mmol) were taken up in benzene (2 mL) and heated to reflux for 48 h. The resin was filtered and washed repeatedly with CH_2Cl_2 and MeOH, and dried in vacuo. ^{13}C NMR ($CDCl_3$, δ): 176.0, 145.2, 142.6, 130–120 (polymer phenyls), 110.2, 109.2, 90.4, 80.9, 71.4, 50.8, 45–38 (polymer backbone), 44.3, 38.8, 29.4, 27.5, 26.4, 25.5. IR (KBr): 1770 cm^{-1}.
Typical method for the ring opening of resin-bound epoxides: resin **7b** (100 mg) and magnesium perchlorate (110 mg, 0.5 mmol) were stirred in 9:1 CH_2Cl_2–CH_3CN, 10 min, after which time the amine (20 equiv) was added. The reaction mixture was stirred at room temperature for 48–96 h. The polymer was filtered and washed with CH_2Cl_2, CH_3CN, MeOH, water, and MeOH, and then dried under vacuum.
General method for the cleavage of resin-bound species: the substituted resin was taken up in approximately 100 mL of toluene and heated to reflux for 12 h. After cooling to room temperature the solvent was filtered away from the polymer and evaporated yielding the free maleimide. Overall yields for the three steps (Diels–Alder attachment, epoxide ring opening, resin cleavage) from **6** were in excess of 80%; product purities were established by NMR and HPLC.
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