Pergamon

Tetrahedron Letters 41 (2000) 7875–7878

TETRAHEDRON
LETTERS

Solid phase Diels–Alder/retro Diels–Alder reactions. A new method for traceless linker strategy

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Received 18 July 2000; accepted 14 August 2000

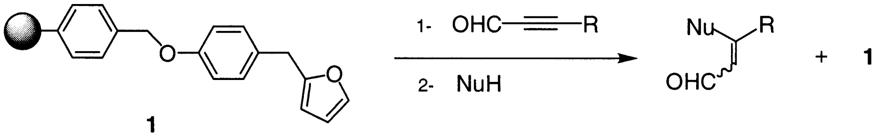
Abstract

A resin-bound furan has been efficiently synthesized from Merrifield resin. This new polymer reacts with an acetylenic dienophile to afford a thermally stable Diels–Alder adduct. Transformation of the adduct by Michael reaction with thiophenol has allowed an easy retro Diels–Alder reaction. This 'safety-catch' procedure leads to the formation of a chemically and stereochemically pure alkene and to the regeneration of the polymer-bound furan. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: solid support; Diels–Alder reactions; cycloreversions; Michael reactions.

In recent years the emergence of combinatorial chemistry as a means to generate libraries of small organic molecules for drug discovery has prompted great interest in the development of new solid phase synthetic methodologies.[1] One interesting aspect of this solid phase chemistry involves the design of reaction sequences which entailed the 'traceless cleavage' of the product from the polymeric support on which it has been elaborated: for example, formation of a C–H bond in place of a C–Si bond,[2] cyclization-assisted cleavage[3] or even cycloreversion.[4]

The Diels–Alder reaction, one of the most efficient reactions for the formation of C–C bonds and the control of stereogenic centers, is now more adapted to solid phase synthesis.[5] In this paper, we describe a new 'traceless' methodology involving the Diels–Alder cycloaddition of a polymer-bound furan **1** with an acetylenic dienophile. In a typical 'safety-catch' procedure, a transformation of the adduct allows a cycloreversion regenerating the resin **1** and giving rise to a functionalized olefin as described below.



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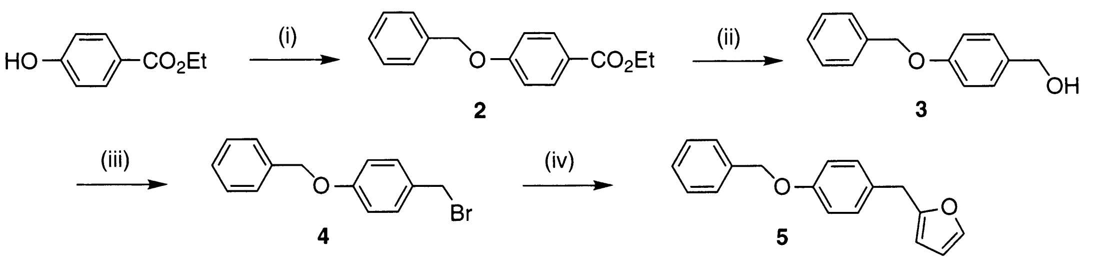
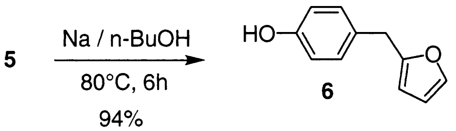
PII: S0040-4039(00)01394-0

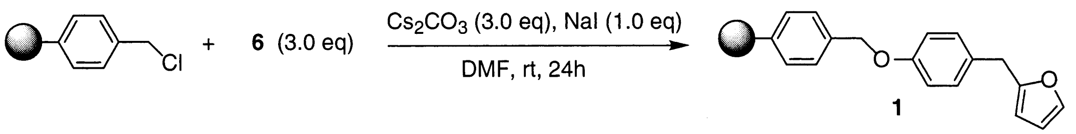
The feasibility of the chemistry was first examined and optimized in solution and then applied to solid phase reactions. The soluble furan **5**, a mimic of the furan-spacer appendage linked to the polymeric chains of **1**, was prepared in 84% overall yield from commercial ethyl 4-hydroxybenzoate as depicted in Scheme 1.[6]



Scheme 1. Reagents and conditions: (i) BrBn, K_2CO_3, Aliquat® 336 (0.01 equiv.), 100°C, 6 h, 98%; (ii) LAH (1.5 equiv.), Et_2O, 0°C then rt, 2 h, 100%; (iii) PBr_3, CH_2Cl_2, 0°C→rt, 15 h, 91%; (iv) (1.7 equiv.), Et_2O/THF, −40°C→rt, 15 h, 94%

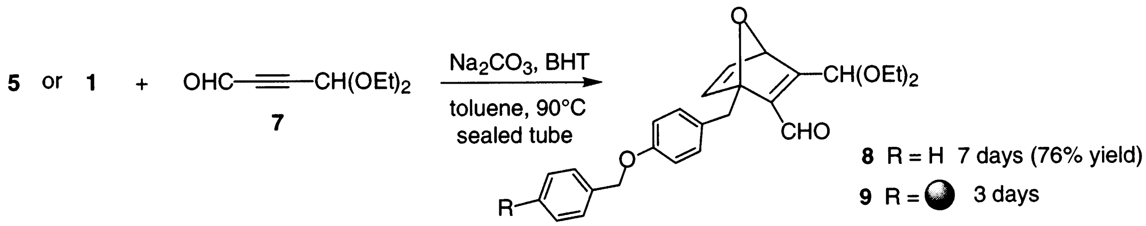
The supported furan **1** was then synthesized by condensation in basic conditions of Merrifield resin[7] with the phenol **6** obtained after hydrogenolysis of the compound **5**.[8]





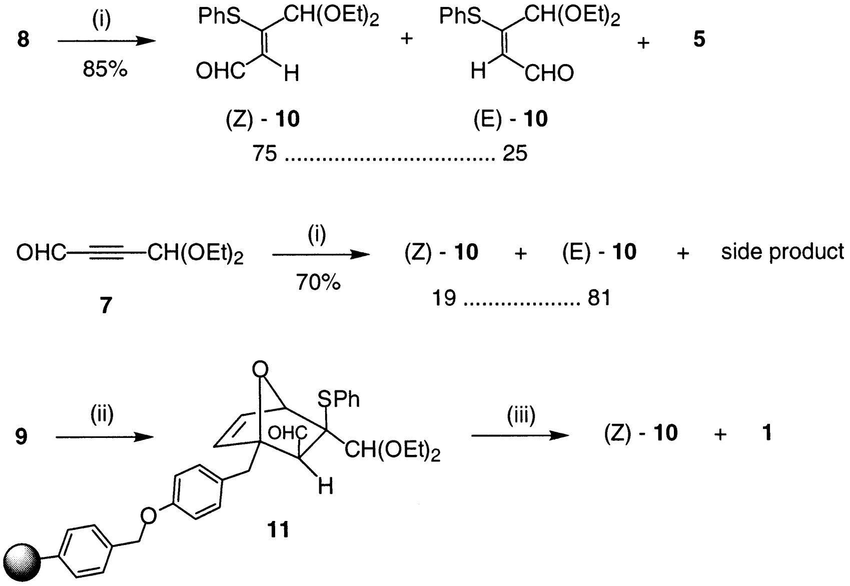
The course of the reaction was followed by IR spectroscopy: observation of the disappearance of the band ν_{C-Cl} at 1265 cm^{-1} and the appearance of a broad band at 1230 cm^{-1} (ν_{Ar-OC}) and characteristic bands of the furan group at 1508 and 1008 cm^{-1}. The polymer **1** was purified by successive washings with DMF, H_2O, DMF, acetone and CH_2Cl_2 and was dried under vacuum. The excess of phenol **6** was recovered after acidification of the filtrates. The structure of the polymer-supported furan **1** was in agreement with the ^{1}H and ^{13}C MAS NMR spectra.[9]

The cycloaddition of **5** with 4,4-diethoxybut-2-ynal **7**[10] (1.1 equiv.) without solvent[11] gave the cycloadduct **8** in 93% yield. Since in solid phase it is necessary to swell the resin, different solvents were tried and the best results were obtained when heating a degassed toluenic solution in a sealed tube at 90°C.[12]



The addition of small amounts (0.1 equiv.) of 2,6-di-*tert*-butyl-4-methylphenol (BHT) and Na_2CO_3 prevented the formation of polymers and a side product resulting from acid-catalyzed addition of furan **5** to the ynal **7**. Under the same conditions but using 4.0 equivalents of **7** and 0.4 equivalents of BHT and Na_2CO_3, the polymer-supported furan **1** afforded the cycloadduct **9** as shown by the presence of a strong band at 1663 cm^{-1} ($\nu_{C=O}$) in the IR spectrum. In both cases only one regioisomer was formed. The configuration of **8** was proved by NOESY experiments. The presence of a similar set of ^{13}C NMR signals in the spectra of the adducts **8** and **9** (MAS NMR)[9] indicates that the two reactions occurred with the same regioselectivity.

The adducts **8** and **9** were thermally stable but when the conjugated double bond was converted into a single bond, cycloreversion occurred even at very low temperatures. The product of Michael addition of PhSH to **8** in the presence of a catalytic amount of PhSNa (Scheme 2) could not be isolated and gave a mixture of furan **5** and of two diastereomeric olefins (*Z*)-**10** and (*E*)-**10** in a ratio $Z/E=75/25$ as shown by ^1H NMR. The relative configuration of the *Z*-isomer was confirmed by NOE experiments. It must be noted for comparison that under the same conditions, the addition of PhSH to 4,4-diethoxybut-2-ynal **7** (Scheme 2) gave the same alkenes **10** but in a different ratio ($Z/E=19/81$) together with a side product.



Scheme 2. Reagents and conditions: (i) PhSH (3.0 equiv.), NaH (0.3 equiv.), THF, −78°C→0°C then treatment by NaOH at 0°C; (ii) PhSH (5.0 equiv.), NaH (0.4 equiv.), THF, −40°C→−35°C then −35°C, 22 h; (iii) filtration and washing with THF, THF/MeOH, THF at −35°C then −35°C→−2°C, 15 h

The addition of PhSH to the resin **9** occurred at low temperature leading to **11**, which is stable up to −35°C (Scheme 2). After being washed at −35°C with THF and THF/MeOH in order to remove the reagents, the resin **11** in suspension in THF was allowed to warm up to −2°C and stirred overnight at this temperature. Filtration gave back the resin **1**, which can be recycled in the same process. Concentration in vacuo of the filtrate left the chemically pure trisubstituted enal (*Z*)-**10** in an excellent 49% overall yield based on Merrifield resin for the four steps sequence.

In conclusion we have shown that the strategy Diels–Alder reaction/cycloreversion on solid support presents several advantages as compared to the same strategy in solution: far better selectivity, high chemical purity, easy recovery and recycling of the starting resin. Applications of this methodology to the synthesis of various substituted olefinic compounds is currently under investigation.

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6. **Caution!** The bromide **4** is a highly allergenic compound.
7. Merrifield resin (200–400 mesh) from Fluka crosslinked with 1% of DVB; loading 0.8 mmol Cl/g.
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9. Selected ^{13}C MAS NMR (100.7 MHz; $CDCl_3$) data: **1** δ 141.5, 129.8, 114.9, 110.3, 106.1, 70.1, 33.7; **9** δ 188.1, 171.7, 157.7, 151.5, 145.2, 143.1, 131.2, 114.4, 97.8, 96.0, 82.6, 69.9, 62.1, 61.6, 34.8, 15.1.
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12. This reaction is extremely air-sensitive: when the same reaction was run under argon in a round-bottomed flask equipped with a condenser using a toluenic solution where argon was previously bubbled, we found only polymeric compounds and the product resulting from Michael addition of furan **5** to the ynal **7**.