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Radical Cyclization on Solid Support: Synthesis of γ-Butyrolactones

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Abstract

Synthesis of γ–butyrolactones using radical cyclization on solid-phase has been achieved. Polymer-supported β-bromoethylacetals were treated with tributyltin hydride in the presence of a catalytic amount of α,α'-azobisisobutyronitrile to generate intermediate carbon radicals which cyclize onto the intramolecular carbon-carbon double bond. The cyclization products were released by Jones oxidation from resin to give γ-butyrolactones in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

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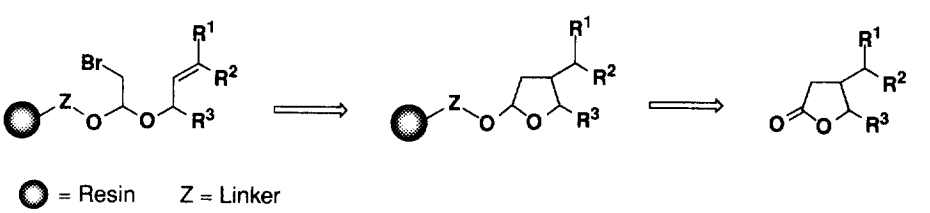
Recently, a variety of useful solution-phase reactions have been applied to the reactions on solid phase since combinatorial chemistry has been recognized as powerful technology for creating a large number of compounds to be biologically evaluated.[1] Development of carbon-carbon bond formation on solid phase is an important task as well as peptide synthesis, aromatic substitution, oxidation, reduction, etc. Some effective methodologies for carbon-carbon bond formation, *e.g.*, cross-couplings, condensations, Michael reactions and Grignard reactions, have so far been studied on solid phase.[2] Recently, study on radical carbon-carbon bond formation on solid phase such as allylation and cyclization has been undertaken[3] although radical reactions have been relatively undeveloped on solid phase. The radical reaction has been recognized as an attractive method for construction of organic molecules, and the characteristic advantages such as high extent of reactivity,

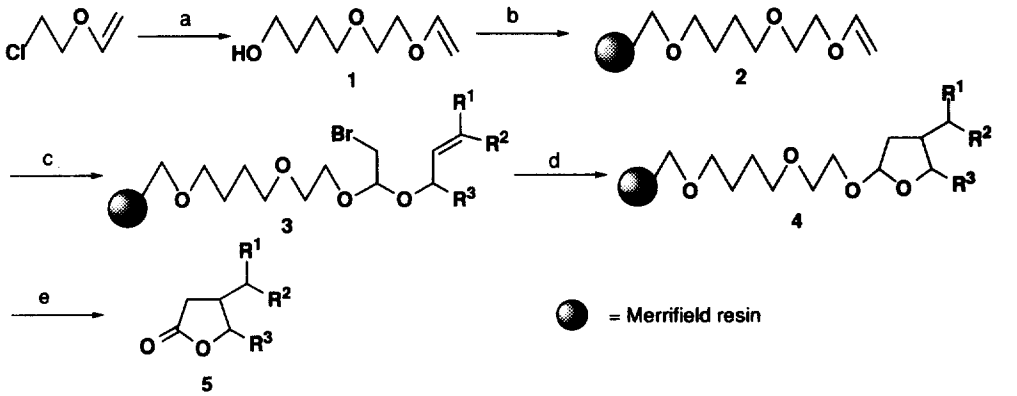


Scheme 1

PII: S0040-4039(99)00503-1

regioselectivity, and stereoselectivity would be promising for natural product syntheses.[4]

In the course of our studies on solution-phase radical reaction,[5] we report herein a convenient synthesis of γ-butyrolactones using the solid-phase radical reaction. Our strategy consists of the radical cyclization of the β-bromoacetals leading to the cyclic acetals[6] on solid support and subsequent cleavage of the cyclization products from the solid-phase by Jones oxidation releasing of γ-butyrolactones (Scheme 1).

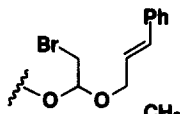
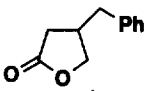
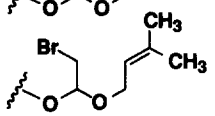
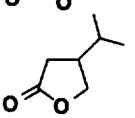
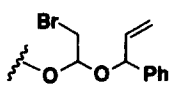
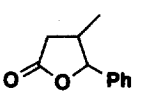
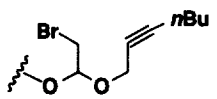
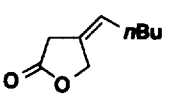
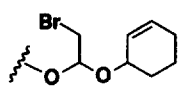
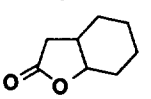
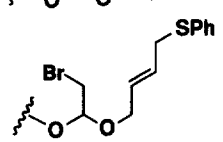
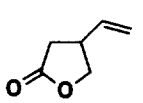


a) NaH (2 equiv), 1,4-butanediol (5 equiv), THF, reflux, 20 h, 82%. b) NaH (3 equiv), Merrifield resin, THF, reflux, 3 days, 84%. c) NBS (5 equiv), allylalcohol (30 equiv), 0 °C, 6 days. d) tributyltin hydride (5 equiv), AIBN (0.5 eq), benzene, reflux. e) Jones reagent (2 equiv), r.t., 3 h.

Scheme 2

At first, a highly efficient preparation of the resin **3** was carried out in three steps, in which a linear spacer separates the polystyrene support from the reactive site[7] (Scheme 2). A mixture of chloroethyl vinyl ether, 1,4-butanediol and NaH in THF was refluxed for 20 h to give the vinyl ether **1** in 82% yield. Merrifield resin[8] was then converted to the resin **2** in 84% yield[9] by treatment with the vinyl ether **1** in the presence of NaH. A series of substrates **3a-e** bearing various β-bromoacetals[10] were prepared by treating resin **2** with NBS (5 equiv) and the corresponding allyl alcohol (30 equiv) in CH_2Cl_2 at 0 °C. Loading yields of resins **2** and **3** were determined by the increase in weight after each reaction in comparison with the weight of the starting resins, and were typically 68-92%.[11] The radical cyclization was carried out by treatment with 5 equiv of tributyltin hydride in the presence of a catalytic amount of α,α'-azobisisobutyronitrile (AIBN) (0.5 equiv) in benzene at 80 °C. Following is a typical experimental procedure for cyclization of **3a** and subsequent oxidative cleavage of the cyclization product from the solid-phase. To a suspension of the bromoacetal resin **3a** (150 mg, 0.162 mmol loaded substrate) in benzene (8 ml) was added Bu_3SnH (215 μl, 0.799 mmol, 5 equiv) and a catalytic amount of AIBN (13.3 mg, 0.081 mmol, 0.5 equiv), and the mixture was stirred for 18 h at 80 °C. The resin **4** was washed succesively with hexane (5 x 3 ml), CH_2Cl_2 (5 x 3 ml), and ether (2 x 3 ml). Analytical samples were dried under vacuum for 12 h. To a suspension of the resin **4** (132.1 mg) in acetone (1.6 ml) was added Jones reagent (2.0 mol/l, 0.34 ml, ca. 5 equiv), and the mixture was stirred for 3 h at room temperature. Then, an excess amount of Jones reagent was consumed by adding 2-propanol. The reaction mixture was neutralized with aq. $NaHCO_3$, filtered, and the solid was washed with CH_2Cl_2 (3 x 5 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 5 ml). The combined organic

Table. Synthesis of the Bromoacetal Resins and Lactones[12]

	Resin 3	Yield of 3[a)]	Lactone 5	Yield of 5[b)]
a		92%		67% (36%)
b		72%		93% (43%)
c		73%		81% (36%) *trans* : *cis* = >99 : 1
d		69%		47% (23%) *E* : *Z* = *10* : *90*
e		68%		61% (26%) *trans* : *cis* = 1 : >99
f		85%		62% (36%)

[a] Yields based on the vinyl content of the resin 3. [b] Isolated yields based on the resin 3. Yields based on Merrifield resin are shown in parentheses.

solutions were dried over Na_2SO_4 and concentrated to give the γ-butyrolactone **5a** (67% yield) which was purified by column chromatography, if neccesary. The results of the cyclization on polymer support followed by Jones oxidation are shown in Table. Cyclization occurred at the internal carbon of the double bond, and no six-membered ring was formed. The stereochemistry of the 2,3-disubstituted lactone **5c** was trans (*trans*:*cis* = >99:1), which was determined by the ^1H nmr spectrum. Cyclization also proceeded on the triple bond to give the lactone **5d** in 47% yield[13] in a ratio of *E*:*Z* = 10:90. The cis bicyclic lactone **5e** was obtained in 61% yield. Radical cyclization of **3f**, followed by β-elimination of the phenylthiyl radical and subsequent Jones oxidation afforded 3-vinyl-γ-butyrolactone **5f** in 62% yield.

An organotin method sometimes results in low yields, which may be caused by the purification procedure to remove the somewhat troublesome tin reagents or tin byproducts from the reaction mixture. This polymer-supported radical cyclization has advantages over its solution-phase reaction. Isolation of the product is easy and purification of the cyclization products is not required for Jones oxidation. In particular, insoluble polymer-supports could be separated easily from the reaction mixture by simple washing and filtration.[14] It is not neccesary to perform the radical cyclization under high dilution conditions presumably due to the polymer effect, and use of an excess amount of tributyltin hydride does not cause contamination of the reduction products.[6] In addition, oxidation of the acetals by Jones reagent concurrently releases the lactones from the polymer support. In

summary, we have demonstrated that radical cyclization of β-bromoethylacetal can be performed on solid support and oxidative cleavage by Jones reagent gave γ-butyrolactones in good yields.

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[2] Hermkens PHH, Ottenheijm HCJ, Rees D. Tetrahedron 1996;52:4527-4554 and references sited therein.

[3] (a) Routledge A, Abell C, Balasubramanian S. Synlett 1997:61-63. (b) Du X, Armstrong RW. J. Org. Chem. 1997;62:5678-5679. (c) Du X, Armstrong RW. Tetrahedron Lett. 1998;39:2281-2284. (d) Berteina S, Mesmaeker AD Tetrahedron Lett. 1998;39:5759-5762. (e) Sibi MP, Chandramouli SV Tetrahedron Lett. 1997;38:8929-8931.

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[6] For radical cyclization of bromoacetals using Bu_3SnH in solution, see: Stork G, Mook R. J. Am. Chem. Soc. 1983;105:3720-3722.

[7] Competitive hydrogen abstraction from the benzylic positions of Merrifield resin or polyether spacers of TentaGel might occur in the radical reactions on solid support, see: 3a

[8] Merrifield resin (2-2.5 mmol/g, 200-400 mesh) from Acros organics was used in all of the experiments. All resins were pre-swelled in the reaction solvent before use.

[9] Yield was based on the Cl content of Merrifield resin. The content of the vinyl moiety in the resin **2** was estimated to be 1.53 mmol/g.

[10] β-Bromoacetals were prepared according to the modified procedure reported in the literature, see: (a) Ueno Y, Chino K, Watanabe M, Moriya O, Okawara M. J. Am. Chem. Soc. 1982;104:5564-5566. (b) Ueno Y, Moriya O, Chino K, Watanabe M, Okawara M. J. Chem. Soc., Perkin Trans. 1 1986:1351-1356.

[11] The reactions have not been optimized for each substituent.

[12] The cyclization products were characterized by the ^1H nmr and ir spectra. The analysis of the substrate on resin was carried out by the ir spectrum.

[13] Formation of neither 2-hexynal nor 2-hexynyl acetate was observed by tlc and gas chromatography after cleavage by Jones oxidation.

[14] Several procedures have been reported to achieve the effective separation of organotin species from the products. (a) Saigo K, Morikawa A, Mukaiyama T. Bull. Chem. Soc. Jpn. 1976;49:1656-1658. (b) Berge JM, Roberts SM. Synthesis 1979:471-472. (c) Leibner JE, Jacobus J. J. Org. Chem. 1979;44:449-450. (d) Curran DP, Chang C. J. Org. Chem. 1989;54:3140-3157. (e) Crich D, Sun S. J. Org. Chem. 1996;61:7200-7201. (f) Renaud P, Lacote E, Quaranta L. Tetrahedron Lett. 1998;39:2123-2126. Organotin compounds on polymer supports have been reported. (f) Crosby NM, Wong GA. J. Org. Chem. 1975;40:1966-1971. (g) Schumann H, Pachaly B. Angew. Chem. Int. Ed. Engl. 1981;20:1043-1044. (h) Dumartin G, Pourcel M, Delmond B, Donard O, Pereyre M. Tetrahedron Lett. 1998;39:4663-4666.