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# Palladium(0)-Catalyzed Cyclization Reaction of Polymer-Supported Aryl Iodides with 1,2-Allenyl Carboxylic Acids. A Facile Solid-Phase Synthesis of Butenolides[†]

**Shengming Ma,* Dehui Duan, and Zhangjie Shi**

*Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry,
Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China*

*masm@pub.sioc.ac.cn*

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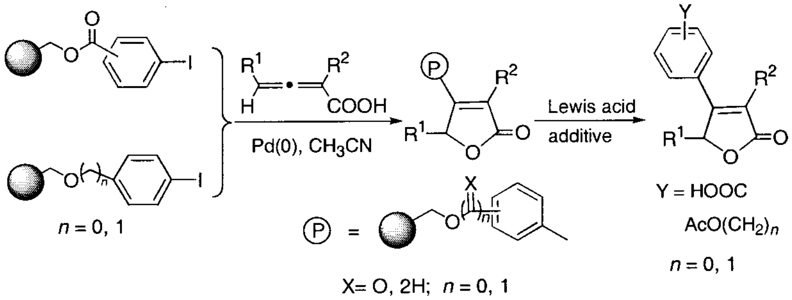
## ABSTRACT



**Aryl iodides anchored to Merrifield resin via the linkages between a carboxyl, hydroxyl, or hydroxymethyl group and the benzylic chloride moiety in the resin reacted efficiently with 1,2-allenic carboxylic acids under the catalysis of Pd(0) to afford polymer-supported butenolides. Polysubstituted butenolides can be easily cleaved from the resins by Lewis acid-catalyzed processes in good yields and purities.**

Combinatorial chemistry has been applied most commonly to identify lead compounds/novel materials[1] and new catalytic processes.[2] One of the most important approaches to the combinatorial synthesis of small molecules is solid-phase organic synthesis (SPOS) due to the potential of automation.[3] Butenolide-containing natural products, which exhibit broad biological activities,[4] have been successfully prepared via solution-phase synthesis in satisfactory yields by our group and others.[5] However, for the construction of libraries of these compounds, the strategy in the solution is time-consuming and unable to be automated. To the best of our

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[†] China Patent Pending (00115358.7).

(1) For recent references on combinatorial chemistry, see: (a) Bunin, B. A. *The Combinatorial Index;* Academic Press: San Diego, 1998. (b) Lam, K. S.; Lebl, M.; Krchňék, V. *Chem. Rev.* **1997**, *97*, 411. (c) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(2) For some of the most recent examples applying combinatorial chemistry to catalyst screening, see: (a) Kagan, H. B. *J. Organomet. Chem.* **1998**, *567*, 3. (b) Gao, X.; Kagan, H. B. *Chirality* **1998**, *10*, 120. (c) Bein, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 323. (d) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180. (e) Cong, P.; Doolen, R. D.; Fan, Q.; Giaquinta, D. M.; Guan, S.; McFarland, E. W.; Poojary, D. M.; Self, K.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 484.

(3) For recent reviews on SPOS, see: (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549. (b) James, I. W. *Tetrahedron* **1999**, *55*, 4855. (c) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293. (d) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

(4) Brima, T. S. U.S. Pat. 4,968,817, 1990; *Chem. Abstr.* **1991**, *114*, 185246y. Tanabe, A. Jpn. Kokai Tokyo Koho, JP 63,211,276 [88,211, 276], 1988; *Chem. Abstr.* **1989**, *110*, 94978q. Lee G. C. M. Eur. Pat. EP 372,940, 1990; *Chem. Abstr.* **1990**, *113*, 191137j. Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S.; Thrien, M. PCT Int. Appl. WO 95,00,501, 1995; *Chem. Abstr.* **1996**, *124*, 55954y. Lee Gary, C. M, Gast, M. E. PCT Int. Appl. WO. 91 16,055, 1991; *Chem. Abstr.* **1992**, *116*, 59197m.

(5) (a) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. (b) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137. (c) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. (d) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387. For a summary of known synthetic methodologies of butenolides, see the corresponding references therein.

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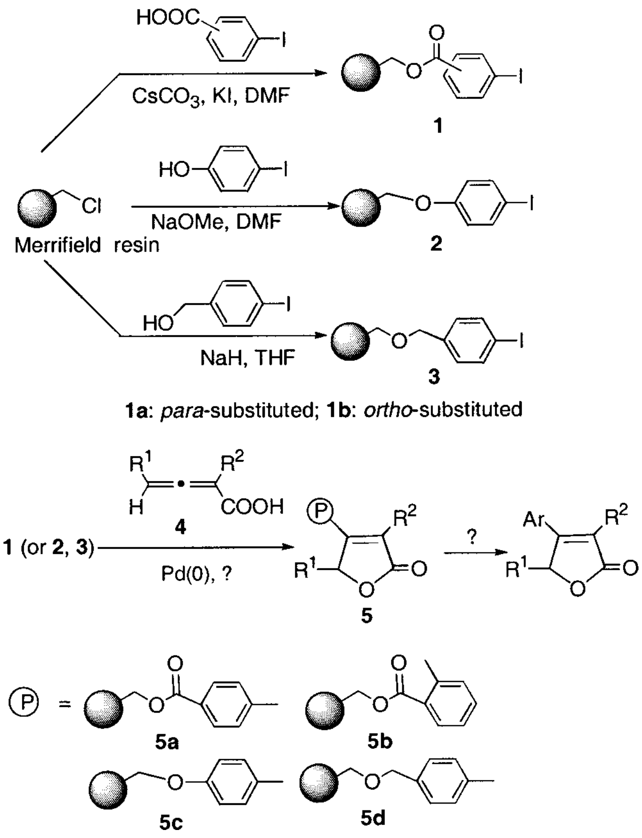
knowledge, no SPOS method has been attempted for the synthesis of butenolides so far. Herein, we wish to report a facile solid-phase synthetic approach to polysubstituted butenolides based on the easily available Merrifield resin and a recently developed methodology[5d] (Scheme 1). Here the following two challenges would be the key to the success of this protocol: (1) Pd(0)-catalyzed solid-phase cyclization of 2,3-dienoic acids and the polymer-bounded aryl iodides; (2) chemoselective cleavage of the linkages while the ester groups in lactones must remain intact.

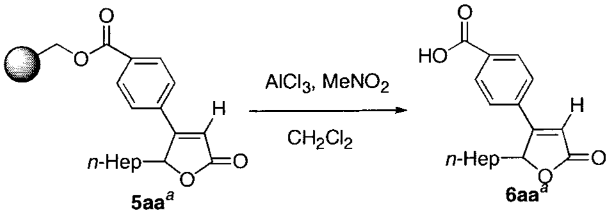
**Scheme 1**



*p*- and *o*-iodobenzoic acids were anchored to the commercially available Merrifield resin[6] to provide resins **1a** and **1b**, respectively.[7] Resin **2**, with a phenolic ether linkage, was obtained by the reaction of *p*-iodophenol and Merrified resin.[8] Merrifield resin was also converted to resin **3** with a benzylic ether linkage by its treatment with *p*-iodobenzyl alcohol using NaH as base.[9]

With some preliminary results on the solid-phase cyclization in hand, we first focused our attention on cleavage of the butenolide moiety from the solid-phase resin **5aa** to establish the evaluation method (Scheme 2). When NEt$_3$ in MeOH/DMF[10] and 50% TFA/CH$_2$Cl$_2$[11] were adopted, no cleavage took place. The cleavage with LiOH[12] or K$_2$CO$_3$[13] gave some unidentified acyclic products. The products from the cleavage with NaOMe[7] were also unidentified. Fortunately, when we used AlCl$_3$ in MeNO$_2$/CH$_2$Cl$_2$ (method A),[14] the expected butenolide **6aa** was obtained cleanly from the resin **5aa**. The concentration and number equivalents of AlCl$_3$ are important to the yields and purities of final products. Four to six equivalents of AlCl$_3$ (0.3−0.5 M) gave the best result.[15,16]

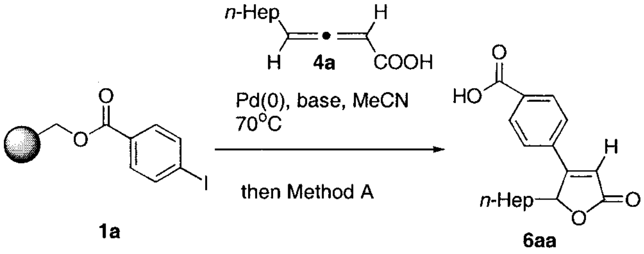
**Scheme 2**



[a] Key to the labeling of compounds **5** and **6**: the first letter refers to the aryl iodide used and the second letter refers to the acid used. Same for Scheme 3 and Tables 1 and 2

When the reaction conditions reported in ref 5d were applied to SPOS of butenolides, we obtained very poor results (entries 1 and 3, Table 1). We reasoned that the choice of the base might be crucial to the solid-phase reaction. In

**Table 1.** Pd(PPh$_3$)$_4$-Catalyzed Cyclization Reaction of Polymer-Supported *p*-Iodobenzonic Acid **1a** with 2,3-Undecadienoic Acid **4a**



| entry | base | **4a** (equiv) | Pd(PPh$_3$)$_4$ (mol %) | time (d) | yield of **6aa** (%)[b,c] | purity (%)[d] |
|---|---|---|---|---|---|---|
| 1 | K$_2$CO$_3$[a] | 3 | 10 | 2 | 33 | 52 |
| 2 | *i*-Pr$_2$NEt | 3 | 10 | 2 | 55 | 51 |
| 3 | K$_2$CO$_3$[a] | 4 | 15 | 3 | 50 | 26 |
| 4 | *i*-Pr$_2$NEt | 2 | 15 | 3 | 49 | 82 |
| 5 | *i*-Pr$_2$NEt | 3 | 15 | 3 | 66 | 88 |
| 6 | *i*-Pr$_2$NEt | 4 | 10 | 3 | 81 | 94 |
| 7 | *i*-Pr$_2$NEt | 4 | 10 | 2 | 77 | 97 |
| 8 | *i*-Pr$_2$NEt | 4 | 15 | 1 | 33 | 95 |
| 9 | *i*-Pr$_2$NEt | 4 | 15 | 2 | 90 | 96 |
| 10 | *i*-Pr$_2$NEt | 6 | 20 | 4 | 85 | 65 |
| 11 | *i*-Pr$_2$NEt | 6 | 20 | 3 | 94 | 89 |
| 12 | *i*-Pr$_2$NEt | 4 | 15 | 3 | 99 | 93 |

[a] 5 mol % of Ag$_2$CO$_3$ based on the acid **4a** was added. [b] On the basis of the maximum loading of the aryl iodide on resin (1.64 mequiv/g). [c] Overall yields from **1a** to **6aa** (method A, see text). [d] Determined by HPLC.

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(6) Merrifield resin (2−2.5 mequiv/g, 200−400 mesh) from Acros Organics was used in all of the experiments. All resins were preswelled in the reaction solvent before use.

(7) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177.

(8) Li, W.-R.; Yo, Y.-C. *Tetrahedron Lett.* **1999**, *40*, 9085.

(9) Watanabe, Y.; Ishikawa, S.; Takao, G.; Toru, T. *Tetrahedron Lett.* **1999**, *40*, 3411.

the presence of $K_2CO_3$ and a catalytic amount of $Ag_2CO_3$, it was the three-phase system (i.e., solid−solution−solid) that hindered the process. Indeed, after some screening we found that when *N*,*N*-diisopropyl-*N*-ethylamine was used as the base, butenolides were formed in better yields and purities even in the absence of $Ag_2CO_3$ (compare entries 1 with 2, 3 with 4, Table 1). The best results were observed when 4 equiv of acid **4a**, 15 mol % of $Pd(PPh_3)_4$, and 2 equiv of *i*-$Pr_2NEt$ were used (entry 12, Table 1).[17] It is noteworthy that longer time and more allenoic acid/catalyst led to the decrease in yield and purity of **6aa** (entries 10 and 11, Table 1).

The cyclization reaction of polymer-bound resins **2** and **3** with ether linkages can also undergo a Pd(0)-catalyzed cyclization reaction to afford polymer-supported butenolides as monitored by FT-IR spectra.[16] The cleavage of the ether linkage provided another challenge because of the relatively more stable ether linkage. Inspired by the above successful cleavage of the ester linkage, we believe that the lactone moiety in butenolides could tolerate the action of some Lewis acids, which may be also of choice for the selective cleavage of benzyl ether linkages. Therefore, we screened some Lewis acids to cleave the Merrifield resin-bounded ether **5ca** (Scheme 3). $SnCl_4$[18] or $AlCl_3$ only gave a trace of unidentified products. So did other Lewis acids such as $ZnCl_2$, $ZnBr_2$, $FeCl_3$, etc. Successful cleavage was realized with a combination of a Lewis acid and acetyl bromide. While aluminum chloride (0.5 equiv) and acetyl bromide (2.0 equiv) provided product **6ca** in 52% yield and 84% purity, the combination of acetyl bromide and zinc(II) bromide (method B)[8] gave the best result (89% yield, 94% purity, entry 7 of Table 2).[19]

**Scheme 3**

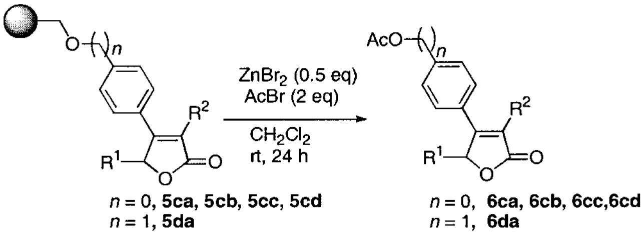
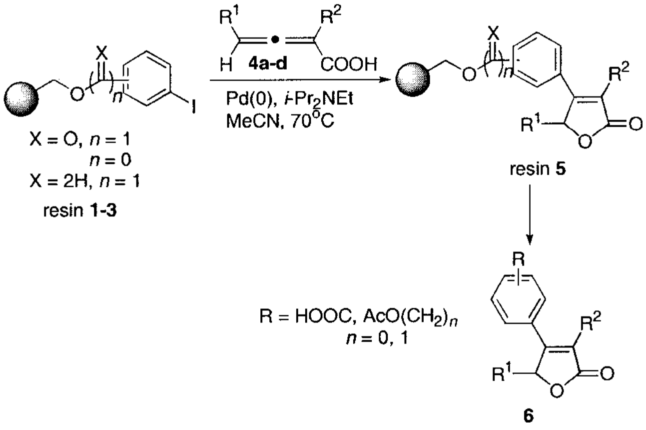


**Table 2.** $Pd(PPh_3)_4$-Catalyzed Cyclization of Polymer-Bounded Aryl Iodides with 1,2-Allenic Carboxylic Acids[a]



| entry | resin 1−3 | $R^1$, $R^2$ (**4**) | resin 5 | method of cleavage[b] | product 6[c] | yield (%)[d] | purity (%)[e] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | *n*-Hep, H (**4a**) | **5aa** | **A** | **6aa** | 99 | 93 |
| 2 | **1a** | *n*-Bu, H (**4b**) | **5ab** | **A** | **6ab** | 93 | 95 |
| 3 | **1a** | c-Hex, H (**4c**) | **5ac** | **A** | **6ac** | ∼100 | 94 |
| 4 | **1a** | *n*-Hex, Me (**4d**) | **5ad** | **A** | **6ad** | 84 | 85 |
| 5 | **1b** | 4a | **5ba** | **A** | **6ba** | ∼100 | 90 |
| 6 | **1b** | 4c | **5bb** | **A** | **6bb** | ∼100 | 96 |
| 7 | **2** | 4a | **5ca** | **B** | **6ca** | 89 | 94 |
| 8 | **2** | 4b | **5cb** | **B** | **6cb** | 87 | 83 |
| 9 | **2** | 4c | **5cc** | **B** | **6cc** | 84 | 87 |
| 10 | **2** | 4d | **5cd** | **B** | **6cd** | 82 | 76 |
| 11 | **3** | 4a | **5da** | **B** | **6da** | 75 | 82 |

[a] All reactions were carried out at 70 °C for 3 days under an argon atmosphere using **1** (or **2**, **3**) (0.15−0.20 mmol), dienoic acid **4** (4 equiv), $Pd(PPh_3)_4$ (15 mol %), and MeCN (4 mL). [b] For method A or B, see text. [c] All new compounds were characterized by $^1H$ NMR, MS(EI), and HRMS spectra. [d] Overall yields from resin **1**−**3** to **6** are based on the maximum loading of aryl iodides on resin. [e] Determined by HPLC.

Stimulated by these results, we studied the solid-phase cyclization and Lewis acid-assisted cleavage process in detail. The results are summarized in Table 2. Several points should be noted. (1) Although the purities were determined by HPLC, they are comparable to the corresponding NMR results. (2) The reactions based on resin **1** gave better yields

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(10) Holmes, D. L.; Smith, E. M.; Nowick, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 7665.

(11) Hetet, C. L.; David, M.; Carreaux, F.; Carboni, B.; Sauleau, A. *Tetrahedron Lett.* **1997**, *38*, 5153.

(12) Chamoin, S.; Houldsworth, S.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4175.

(13) Goldwasser, J. M.; Leznoff, C. C. *Can. J. Chem.* **1978**, *56*, 1562.

(14) Mata, E. G. *Tetrahedron Lett.* **1997**, *38*, 6335.

(15) **Typical procedure of $AlCl_3$-assisted cleavage (method A):** resin **5aa** (67 mg, maximum loading quantity 1.503 mequiv/g) was swelled in $CH_2Cl_2$ (2 mL) for 30 min at room temperature. After cooling to 0 °C, the solution of $AlCl_3$ (0.6 equiv) in $MeNO_2$ (2 mL, 0.3 M, 0.6 mmol) was added and the mixture was stirred for an additional 30 min at the same temperature. The resin was filtered and washed with EtOAc. The filtrate was transferred to a separatory funnel and washed with 0.5 N HCl twice, and the aqueous layer was extracted with EtOAc. The combined extracts were dried and evaporated to give product **6aa** (30 mg, 99% overall yield from Merrified resin based on the maximum loading of aryl iodide and 93% purity).

(16) The whole reaction processes from Merrifield resin to final product were monitored by FT-IR. The loading of iodobenzonic acid to Merrifield resin is indicated by the strong peak at 1720 $cm^{-1}$. It is the two equal strong carbonyl absorptions at 1717 and 1757 $cm^{-1}$ respectively that verified the realization of the solid-phase cyclization reaction (resins **5aa-d** and **5ba-b**). The formation of resins **5ca-d** and **5da** was shown by the existence of a single strong carbonyl peak at 1755 $cm^{-1}$.

(17) **Typical procedure:** to a degassed suspension of the resin **1a** (92 mg, maximum loading 1.636 mequiv/g resin) in dry $CH_3CN$ (4 mL) were added 2,3-undecadienoic acid **4a** (110 mg, 4.0 equiv), *i*-$Pr_2NEt$ (0.21 mL, 8.0 equiv), and $Pd(PPh_3)_4$ (26 mg, 15 mol %) subsequently. The mixture was stirred at 70 °C for 3 days under an argon atmosphere. Then it was cooled to room temperature and filtered. The resin was washed successively with DMF (5 mL × 3), DMF/$H_2O$ (1: 1, 5 mL × 3), $H_2O$ (5 mL × 3), DMF (5 mL × 2), THF (5 mL × 3), and MeOH (10 mL × 3) and then dried under high vacuum overnight to afford resin **5aa** (101 mg, ∼100% overall yield from Merrified resin based on the maximum loading of aryl iodide).

(18) Stones, D.; Miler, D. J.; Beaton, M. W.; Rutherford, T. J.; Gani, D. *Tetrahedron Lett.* **1998,** *39*, 4875.

and purities than those based on resins **2** and **3**, which must stem from the different electronic effects of the carboxy group (resin **1**) and alkoxyl group (resins **2** and **3**) on the aryl rings. (3) The steric effect of aryl iodides is not obvious since the reactions with *para*-substituted resin **1a** and *ortho*-substituted resin **1b** gave similar results (compare entries 5 and 6 with entries 1−4, Table 2). (4) For 2-methyl-2,3-decadienoic acid **4d**, yields and purities were low, which could be ascribed to the lower reactivity of the acid due to the introduction of methyl group (entries 4 and 10, Table 2).

In conclusion, we have developed a high-yielding SPOS route to polysubstituted butenolides using the readily available/cheap Merrifield resin and simple linkers. Although an excess amount of reagents was required, higher yields were achieved as compared to the those of the corresponding solution-phase synthesis.[5d] Considerably simplified workup procedures replace the time-consuming isolation and purification steps in the solution-phase synthesis. In this Letter, only the reactions of alkyl-substituted 2,3-dienoic acids were used; studies on the scope and other types of solid-phase synthesis of butenolides are being carried out in our laboratory.

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**Supporting Information Available:** Analytical data for all products. This material is available free of charge via the Internet at http://pubs. acs.org.

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(19) **Typical procedure of $ZnBr_2$-assisted cleavage (methos B):** resin **5ca** (96 mg, maximum loading quantity 1.56 mequiv/g) was swelled in $CH_2Cl_2$ (4 mL) and treated with $ZnBr_2$ (17 mg, 0.5 equiv) and acetyl bromide (22 $\mu$L, 2.0 equiv) under an argon atmosphere. The mixture was stirred for 24 h at room temperature, and then the resin was collected by filtration. The filtrate was washed successively with 5% $NaHCO_3$, 5% HCl, and a saturated aqueous NaCl solution. The organic layer was dried, filtered, and concentrated to afford product **6ca** (42 mg, 89% overall yield from Merrified resin and 94% purity).