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Tetrahedron Letters 45 (2004) 1511–1513
Tetrahedron Letters

A solid-phase version of the Nozaki–Hiyama allylation of aldehydes with supported allylic bromides

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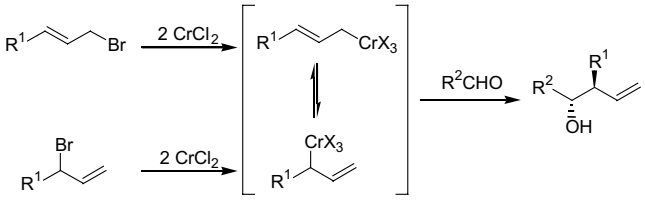
Received 27 October 2003; revised 1 December 2003; accepted 5 December 2003

Abstract—A solid-phase version of the Nozaki–Hiyama allylation of supported allylic bromides with aldehydes is described. α-Methylene γ-butyrolactones **7** can be obtained by cyclization cleavage of the supported intermediate homoallylic alcohols **6**.

Over the last few years, combinatorial chemistry has emerged as a powerful tool in organic synthesis. As a result, the development of new methodology as well as the adaptation of already existing ones to make them amenable to parallel synthesis has become a very active research topic.[1] Solid-phase synthesis is still one of the methods of choice when planning a combinatorial approach, mainly due to the easy separation of reagents and the immobilized substrate during the workup process.[2]

In the course of our research on new aldehyde allylation protocols,[3–6] we were interested in the development of a solid-phase version of the well-known Cr-promoted Nozaki–Hiyama reaction (Scheme 1).[7]

Allylic halides **4a–d** were chosen as suitable models to test our solid-phase approach. They were synthesized from acrylic acid PS-Wang resin **1**[8,9] and aldehydes **2a–d** by a combination of Baylis–Hillman reactions[10] followed by allylic bromination (NBS, Ph_3P, CH_2Cl_2)[11] of the intermediate alcohols **3a–d**[12] (Scheme 2).



Scheme 1. Stereo- and regioselectivity of the Nozaki–Hiyama reaction.

As also observed in control reactions in the solution phase, bromination took place with allylic rearrangement. However, the regioselectivity of this step was not essential for the overall process, due to the well-known regioconvergence of the Nozaki–Hiyama allylation reaction (see Scheme 1).[7]

With allylic halides **4a–d** in hand, we carried out the Nozaki–Hiyama reaction by condensation of **4a** in THF with different aldehydes in the presence of in situ generated Cr^{2+} (freshly prepared from $CrCl_3$ and $LiAlH_4$ in THF), following a classical procedure (Scheme 3).[13,14]

Under these conditions, 'premature' cleavage of adducts **6** was observed, since the putative homoallylic alcohol intermediates spontaneously underwent intramolecular transesterification cleavage to give the corresponding *syn*-lactones **7aa′–7ac′** as the only products.[15,16] However, this drawback could be avoided by carrying out the allylation directly with $CrCl_2$ in DMF.[17,18] Under these experimental conditions, no lactones were detected in the filtrates. Moreover, although traces of Cr by-products were present in the washed resins, these could be properly characterized by gel-phase ^{13}C NMR, where the resonance peak at around 25 ppm of the starting CH_2Br group was no longer present and resonances attributable to the R^2 side chains could be observed. A series of resin-bound allylic alcohols **6** were obtained in

Keywords: Allylation; Chromium; Solid phase; Lactones.
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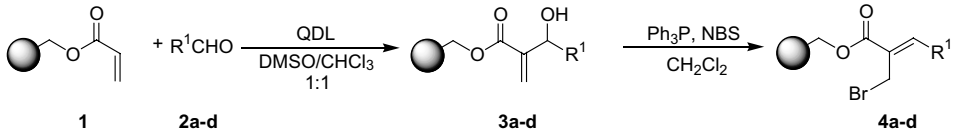
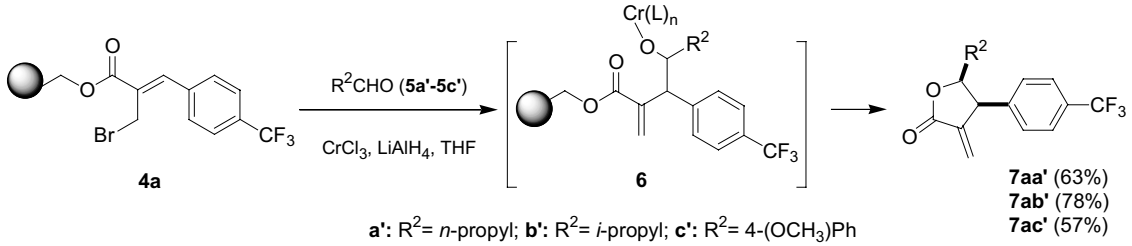
doi:10.1016/j.tetlet.2003.12.017

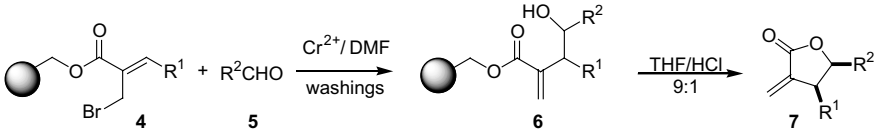


Scheme 2. Synthesis of solid-supported allylic bromides **4a**–**d**.



Scheme 3. Reaction of solid-supported **4a** with different aldehydes in the presence of in situ generated Cr^{2+} in THF (for experimental details, see Ref. 14).

Table 1.



Entry	Resin	R^1	Aldehyde	R^2	Lactone	Yield[a]
1	**4a**	4-(CF_3)Ph	**5a′**	*n*-Propyl	**7aa′**	48
2	**4a**	4-(CF_3)Ph	**5b′**	*i*-Propyl	**7ab′**	51
3	**4a**	4-(CF_3)Ph	**5c′**	4-(CH_3O)Ph	**7ac′**	42
4	**4b**	4-(F)Ph	**5a′**	*n*-Propyl	**7ba′**	45
5	**4b**	4-(F)Ph	**5c′**	4-(CH_3O)Ph	**7bc′**	31
6	**4b**	4-(F)Ph	**5d′**	Allyl	**7bd′**	36
7	**4c**	Ph	**5a′**	*n*-Propyl	**7ca′**	42
8	**4c**	Ph	**5c′**	4-(CH_3O)Ph	**7cc′**	37
9	**4c**	Ph	**5d′**	Allyl	**7cd′**	54
10	**4d**	*n*-Propyl	**5a′**	*n*-Propyl	**7da′**	35
11	**4d**	*n*-Propyl	**5c′**	4-(CH_3O)Ph	**7dc′**	35
12	**4d**	*n*-Propyl	**5d′**	Allyl	**7dd′**	41

this way (Table 1). In order to test the reactivity of resin-bound allylic alcohols **6**, cyclization cleavage to lactones **7** was investigated for comparative purposes. After several unsuccessful attempts under basic conditions (KO^tBu) or in the presence of a Lewis acid ($BF_3{\cdot}Et_2O$), treatment with THF/concd HCl mixture (9:1) afforded lactones **7**,[17] albeit in lower yields than in the 'one-pot' protocol depicted in Scheme 3 (compare with entries 1–3, Table 1). However, despite the lower overall yields, this two-step protocol has the advantage of keeping the allylation adducts **6** anchored on the solid support for further synthetic manipulations.

In summary, a solid-phase version of the Nozaki–Hiyama allylation of allylic bromides with aldehydes is presented. Although α-methylene γ-butyrolactones **7** are formed in acceptable yields by spontaneous cyclization cleavage from the resin, the intermediate supported homoallylic alcohols **6** can be isolated by proper choice of conditions. Further studies to exploit the synthetic potential of resins **6** will be addressed in the near future and will be reported elsewhere.

Acknowledgements

Financial support from the European Union (contract FMRXCT98-0235), and DURSI Generalitat de Catalunya (2001SGR00342 and 2001SGR00085) is gratefully acknowledged.

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10. General procedure for the Baylis–Hillman reaction: 1.54 g of resin **1**[9] (1.0 mmol/g) was suspended in 13.5 mL of DMSO/$CHCl_3$ (1:1 mixture) in a 25 mL screw-cap bottle. 3-Quinuclidinol (QDL, 574 mg, 4.51 mmol) was weighed directly into the bottle followed by 7.50 mmol of aldehyde **2a**–**d**. The bottle was capped and agitated for cycles of 24 h by mounting it on an incubation tube rotor. After each cycle the reagent solution was removed by inverse filtration and the resin was washed successively with DMSO/$CHCl_3$ 1:1, MeOH, and DMSO/$CHCl_3$ 1:1. At the end of the reaction, the reagent mixture was removed by filtration, the resin was washed successively with DMF, MeOH, DMA, CH_2Cl_2, and MeOH on a filter funnel, and dried under vacuum. The approximate loading was estimated based on resin weight increase. Aldehydes **2a**–**d** required 3 cycles for complete reaction, weight increase of resins **3a**–**d** was higher than 98% of the theoretical loading. For a similar protocol and a general overview of Baylis–Hilman reactions, see: Patra, A.; Roy, A. K.; Joshi, B. S.; Roy, R.; Batra, S.; Bhaduri, A. P. *Tetrahedron* **2003**, *59*, 663–670, and references cited therein.
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12. General procedure for allylic bromination: resins **3a**–**d** (1.3 g, approximate loading 1.0 mmol/g) and Ph_3P (1.7 g, 6.38 mmol) were flushed with argon and suspended in 20 mL of anhydrous CH_2Cl_2. The mixture was cooled to −50 °C and 1.13 g of NBS (6.32 mmol) were added portionwise through a funnel. The funnel was rinsed with 10 mL of anhydrous CH_2Cl_2. After warming to room temperature overnight, the resin was sequentially washed (four times) on a filter funnel with CH_2Cl_2 and MeOH. Drying under vacuum gave resins **4a**–**d**. Completeness of the reaction was assessed by gel-phase NMR by the disappearance of the signal at around 72 ppm (COH) and the appearance of a signal at around 25 ppm (CH_2Br).
13. See Ref. 7a.
14. General procedure for Nozaki–Hiyama reaction of **4a** with aldehydes **5a′**–**5c′** with in situ cyclization cleavage: A solution of aldehyde **5** (1 mmol) in THF (6 mL) was added to resin **4a** (285 mg, approximate loading 0.80 mmol/g) in 1 mL THF. The slurry was treated with the previously formed Cr^{2+} salt, prepared as described in Ref. 7a. After agitating at rt for 18 h, the resin was successively washed with THF, MeOH, and CH_2Cl_2. The combined filtrates were evaporated to dryness and the residue was flash chromatographed (hexanes/Et_2O 4:1) to give lactones **7** (see Scheme 3). **7aa′**: ^{1}H NMR (300 MHz, $CDCl_3$): 0.75 (t, 3H), 0.95 (m, 2H), 1.15 (m, 1H), 1.40 (m, 1H), 4.34 (dt, 1H, $J = 7.8$ Hz, $J' = 2.5$ Hz), 4.67 (m, 1H), 5.54 (d, 1H, $J = 2.4$ Hz), 6.41 (d, 1H, $J = 2.4$ Hz), 7.21 (d, 2H, $J = 7.7$ Hz), 7.56 (d, 2H, $J = 7.7$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): 13.5 (CH_3), 19.0 (CH_2), 34.4 (CH_2), 49.1 (CH), 80.9 (CH), 123.8 (CF_3), 124.7 (CH_2), 125.6 (CH), 129.3 (CH), 129.8 (*C*-CF_3), 138.7 (C_q), 141.8 (C_q), 169.9 (CO). **7ab′**: ^{1}H NMR (300 MHz, $CDCl_3$): 0.67 (d, 3H, $J = 6.6$ Hz), 1.02 (d, 3H, $J = 6.6$ Hz), 1.58 (m, 1H), 4.23 (m, 2H), 5.58 (d, 1H, $J = 1.6$ Hz), 6.35 (d, 1H, $J = 1.6$ Hz), 7.28 (d, 2H, $J = 8.1$ Hz), 7.57 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): 18.0 (CH_3), 18.3 (CH_3), 28.7 (CH), 48.9 (CH), 86.7 (CH), 123.9 (CF_3), 124.2 (CH_2), 125.7 (CH), 128.9 (CH), 130.1 (*C*-CF_3), 140.2 (C_q), 142.8 (C_q), 170.1 (CO). **7ac′**: ^{1}H NMR (300 MHz, $CDCl_3$): 3.65 (s, 3H), 4.68 (dt, 1H, $J = 8.2$ Hz, $J' = 2.8$ Hz), 5.56 (1H, d, $J = 2.8$ Hz), 5.81 (d, 1H, $J = 8.2$ Hz), 6.53 (1H, d, $J = 2.8$ Hz), 6.63 (m, 2H), 6.71 (m, 2H), 6.86 (d, 2H, $J = 7.9$ Hz), 7.34 (d, 2H, $J = 7.9$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 51.7 (CH), 55.2 (CH_3), 82.0 (CH), 113.6 (CH), 124.2 (CF_3), 125.1 (*C*-CF_3), 125.3 (CH), 127.1 (CH), 129.7 (CH), 137.6 (C_q), 140.7 (C_q), 159.5 (C_q), 170.3 (CO).
15. The complete *syn*-stereoselectivity observed, as evidenced by ^{1}H NMR data, is in agreement with the postulated mechanism operating for this allylation process. See: (a) Ref. 7d, p 189; (b) Okuda, Y.; Natatsukasa, S.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 481–484 (c) Drewes, S. E.; Hoole, R. F. A. *Synth. Commun.* **1985**, *15*, 1067–1074.
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    The Cr catalytic version of the Nozaki–Hiyama reaction was tried in order to prevent spontaneous cyclization cleavage by trapping the reactive Cr-alkoxide intermediate as the corresponding silyl ether. Unfortunately, all attempts were unsuccessful and lactones **7** were also obtained from the filtrates in high yields.
17. General procedure for the synthesis of resins **6** and lactones **7** from Nozaki–Hiyama reaction of resins **4** with aldehydes **5**: Anhydrous $CrCl_2$ (200 mg, 1.63 mmol) was added portionwise under a stream of Ar over a slurry of resin **4** (200 mg, approximate loading 0.80 mmol/g) in dry DMF (10 mL). After agitating at rt for 18 h, the resin was washed with DMF, MeOH, and CH_2Cl_2 (three cycles) and dried under vacuum. Resins **6** were checked by ^{13}C NMR (see text) and their loadings (weight gain) were estimated between 0.75 and 0.80 mmol/g, depending on the resin. Resins were stirred in a mixture of THF/2 M HCl (9:1) for 30 min at rt and washed with CH_2Cl_2 and MeOH. The combined filtrates were evaporated and the remaining residues were flash chromatographed (hexanes/Et_2O 4:1) to give lactones **7** (see Table 1).
18. The use of $CrCl_2$ to avoid spontaneous lactonization has already been reported (see Ref. 15c).