Pergamon

Tetrahedron Letters 43 (2002) 5611–5615

TETRAHEDRON LETTERS

Synthesis of 4-pentenoic and 5-hexenoic acids on polystyrene resin and their use as cleavable linkers

MaoJun Guo* and Laszlo Varady

ArQule Inc., 19 Presidential Way, Woburn, MA 01801, USA

Received 23 May 2002; revised 6 June 2002; accepted 10 June 2002

Abstract—Direct synthesis of 4-pentenoic and 5-hexenoic acid derivatives on polystyrene resin was achieved and their use as cleavable linkers in solid phase organic synthesis has been demonstrated.

Since Merrifield introduced solid supports for peptide synthesis,[1] solid phase organic synthesis has been expanded from traditional oligomer synthesis such as peptides, oligonucleotides, and oligosaccharides[2] into small molecules.[3,4]

One inherent part of a solid-phase synthesis is the choice of the linker, which should be stable under the reaction conditions and allow the product to be cleaved from the linker, with mild reagents which can readily be removed. A number of linkers have been developed for solid-phase synthesis based on different strategies.[5,6] Linkers attached to solid support act like protecting groups and indeed a lot of linkers were originated from protecting groups. Recently we reported 2-(3-aminopropyl)-4-pentenoic acid as a biocompatible, cleavable linker for solid phase organic synthesis.[7] The design of this linker was originated from 4-pentenoic acid as a protecting group.[8–10]

Our goal is to further explore linkers based on this 4-pentenoyl group strategy with different variations, such as changing 4-pentenoyl to 5-hexenoyl group, and changing the way the linkers were bound to the polymer from a carbon–nitrogen amide bond to a carbon–carbon bond. Herein we report our preliminary results on the direct synthesis of 4-pentenoic and 5-hexenoic acid derivatives on polystyrene and their use in solid phase organic synthesis.

There are different ways to synthesize 4-pentenoic and 5-hexenoic acid derivatives directly on polystyrene through carbon–carbon bond formation. Scheme 1 outlined a few examples of these synthetic routes using either Merrifield resin[11] or PS-benzaldehyde.[12] Details of these transformations are described below:

Example 1: synthesis of 4-methyl-5-PS-4-pentenoic acid (**3**)

Polystyrene bound triphenylphosphonium chloride (**1**)[13] was suspended in dry THF and treated with potassium *tert*-butyloxide (1.2 equiv.) at room temperature for 1 h. With stirring, ethyl levulinate (1.5 equiv.) was added slowly and the resulted suspension was heated under reflux overnight with stirring. The liquid was drained and the resin was washed sequentially with THF, DMF, toluene and THF to give polystyrene bonded ethyl 4-methyl-4-pentenoate (**2**).

The resin bonded ester (**2**) was then hydrolyzed with Bu_4NOH and converted to free acid with HCl to give 4-methyl-4-pentenoic acid functionalized resin (**3**).[14]

Example 2: synthesis of 2-PS-4-pentenoic acid (**5**)

Ethyl 4-pentenoate was dissolved in THF and treated with 1 equiv. of 2 M butyllithium in pentane for 1 h at room temperature. To the solution, Merrifield resin[15] was added and the resulting suspension was stirred at room temperature overnight. After washing with MeOH, water and DMF, polystyrene bonded intermediate (**4**) was generated.

The resin bonded ester (**4**) was hydrolyzed and converted to free acid as described above to give 4-pentenoic acid functionalized resin (**5**).

* Corresponding author. Tel.: +1 781 994 0416; fax: +1 781 994 0679; e-mail: maojunguo@arqule.com

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01111-5

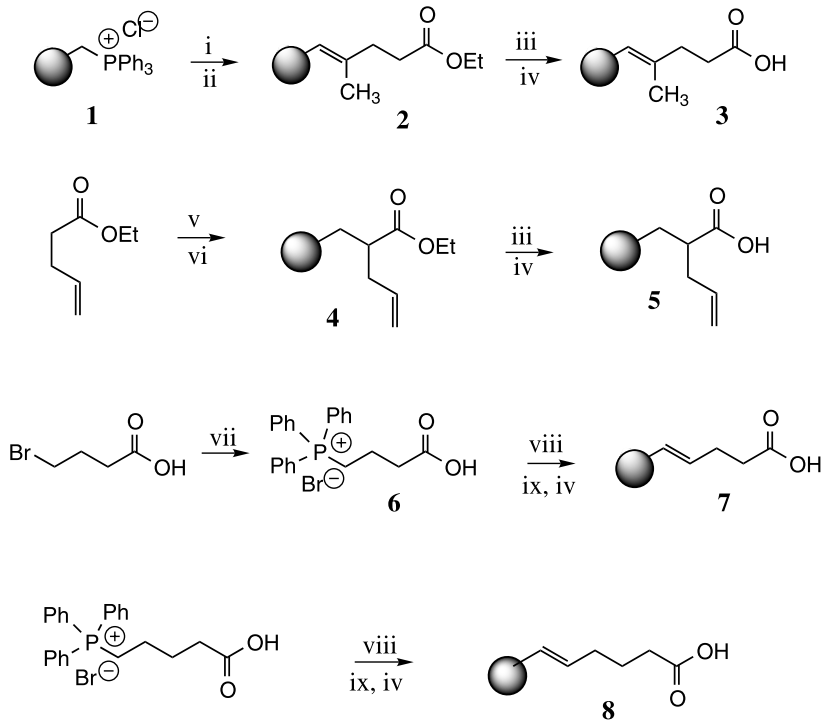
Example 3: synthesis of 5-PS-4-pentenoic acid (**7**) and 6-PS-5-hexenoic acid (**8**)

Either (4-carboxybutyl) triphenylphosphonium bromide or (3-carboxypropyl) triphenylphosphonium bromide (**6**)[16] was dissolved in DMSO and treated with 2 equiv. of 1 M potassium *tert*-butyloxide at room temperature for 1 h. To the solution, PS-benzaldehyde[17] was added and the mixture was stirred at 100°C overnight. Liquid was drained and the resin was sequentially washed twice with MeOH, water, MeOH and THF. The resin was then treated with HCl solution in THF, washed and dried as described before to give 4-pentenoic acid functionalized resin (**7**) and 5-hexenoic acid functionalized resin (**8**), respectively.

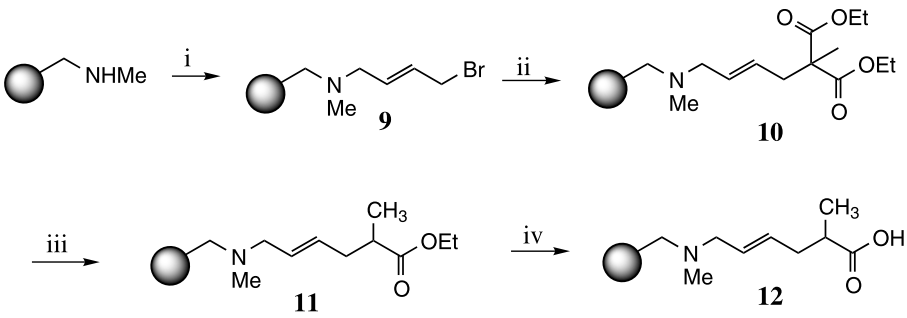
Yet in another way, 4-hexenoic acid derivative can be synthesized on polystyrene through the formation of carbon–nitrogen or carbon–oxygen bonds. One synthetic route is outlined in Scheme 2.

Example 4: synthesis of 2-methyl-6-(*N*-methyl-*N*-PS)-4-hexenoic acid (**12**)

N-Methylaminomethyl polystyrene[18] and 1,4-dibromobutene (5 equiv.) were suspended in DMF and the suspension was kept at 60°C for 18 h with stirring. After draining the liquid, the resin particles were collected on a glass filter and rinsed with MeOH, water, DMF to give intermediate (**9**).



Scheme 1. Synthesis of 4-pentenoic and 5-hexenoic acid linked to polystyrene through a carbon–carbon bond. *Reagents and conditions*: (i) *t*-BuOK/THF, rt, 1 h; (ii) ethyl levulinate, refluxing, 18 h; (iii) Bu_4NOH, MeOH/THF, refluxing, 48 h; (iv) HCl/THF/H_2O, rt, 1 h; (v) *n*-BuLi, THF, rt, 1 h; (vi) Merrifield resin, rt, 18 h; (vii) Ph_3P, THF, refluxing, 72 h; (viii) *t*-BuOK, DMSO/THF, rt, 1 h; (ix) PS-benzaldehyde, 100°C, 18 h.



Scheme 2. Synthesis of 4-pentenoic acid linked to polystyrene through carbon–nitrogen bond. *Reagents and conditions*: (i) 1,4-dibromo-butene, 60°C, 18 h; (ii) diethyl methylmalonate, NaH/DMF, 60°C, 18 h; (iii) LiBr, H_2O, DMF, refluxing, 50 h; (iv) (a) Bu_4NOH, MeOH/THF, refluxing, 48 h; (b) HCl/THF/H_2O, rt, 1 h.

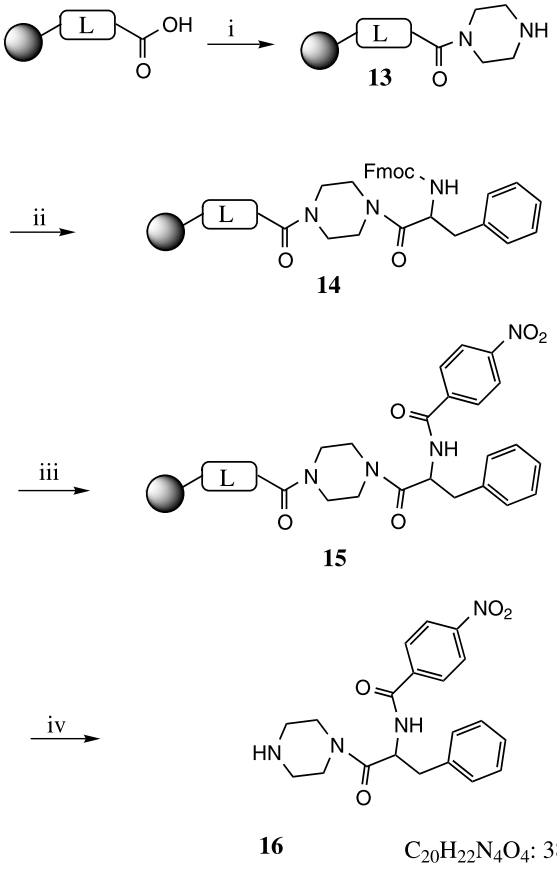
The above resin was suspended in DMF containing diethyl methylmalonate (5 equiv.) and sodium hydride (60% dispersion in mineral oil, 5 equiv.) and heated at 60°C for 18 h. After draining the liquid, the resin particles were collected and rinsed with MeOH, water, DMF to give intermediate (**10**).

The intermediate resin (**10**) was suspended in DMF containing 2 equiv. lithium bromide, 4 equiv. water and heated at 140°C for 50 h. After draining the liquid, the resin particles were collected and rinsed with MeOH, water, MeOH and DMF to give intermediate (**11**).[19]

The resin bonded ester (**11**) was then converted to 2-methyl-4-hexenoic acid functionalized resin (**12**).[14]

In summary, we have developed several simple synthetic routes to synthesize 4-pentenoic, 4-hexenoic and 5-hexenoic acid derivatives directly on polystyrene resin. Next we used these functionalized resins (**3**, **5**, **7**, **8**, **12**) in solid phase organic synthesis to determine whether or not they can be used as cleavable linkers.

Scheme 3 shows a model synthesis using these functionalized resins (**3**, **5**, **7**, **8**, **12**) and details are described below:

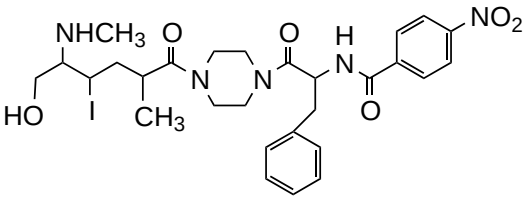


Scheme 3. Solid phase synthesis uses these new linkers and the release of product. *Reagents and conditions*: (i) HOBt, DICD, piperazine, DMF, rt, 18 h; (ii) HOBt, DICD, *N*-Fmoc-phenylalanine, DMF, rt, 18 h; (iii) HOBt, DICD, *p*-nitrobenzoic acid, DMF, rt, 18 h; (iv) 0.1 M iodine in THF/H_2O (4/1), rt, 2 h.

The functionalized resins (**3**, **5**, **7**, **8**, **12**) were added to reaction vials, followed by 4 equiv.[20] of HOBt, diisopropylcarbodiimide and piperazine in DMF. The suspension was shaken at room temperature overnight. After draining the liquid and washing with DMF, the same standard coupling procedure was performed on the resulting resin bound intermediate (**13**) with *N*-Fmoc-phenylalanine in DMF to generate resin bound intermediate (**14**). Fmoc was removed by treating the resin with 10% DBU/DMF at room temperature for 30 min.[21] The resin was washed with DMF and coupled with *p*-nitrobenzoic acid under the same condition to give (**15**). The products were cleaved from the resin by treating with 0.1 M I_2 in THF/H_2O (4/1) for 2 h at room temperature. Excess iodine was reduced with sodium sulfite. After extraction, the products released from the functionalized resins (**3**, **5**, **7**, **8**, **12**) were analyzed by LC–MS and those samples from (**3**, **5**, **7**, **8**) all show up as a single peak with MS corresponding to compound (**16**) (ES+, Found 383.22, M+1).

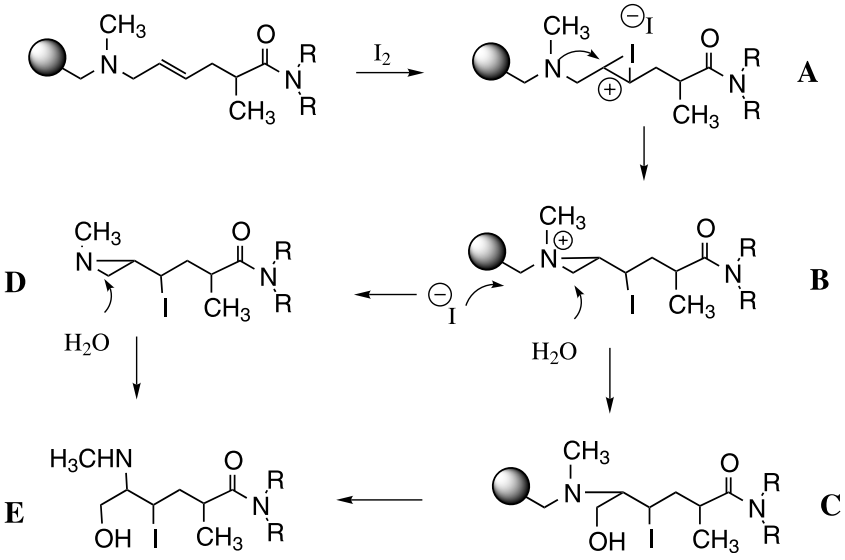
However, LC–MS analysis of the released products from 2-methyl-6-(*N*-methyl-*N*-PS)-4-hexenoic acid (**12**) indicates that compound (**16**) exists only as a minor product from the cleavage. The major product has a different retention time in LC–MS with M+1 found to be 666.20. Normally, the products were released from solid phase through a cycloelimination process.[22] In this case, beside the normal cleavage pathway to give compound (**16**), the existence of *N*-methyl group changed the cleavage reaction to go through other pathway. One mechanism proposed is outlined in Scheme 4.

When the intermediate **A** was formed initially, the tertiary nitrogen acted as a nucleophile and formed the intermediate **B**. Intermediate **B** is either hydrolyzed to give **C**, from which product **E** was released from the solid support by hydrogen iodide generated in situ; or released from the solid support first to give intermediate **D**, which upon hydrolysis gave product **E**. In analogy to product **E** released according to the above proposed mechanism, we assigned the major product released as compound **17**.[23]



17 $C_{28}H_{36}IN_5O_6$: 665.17

In conclusion, we have developed simple and easy synthetic routes to introduce 4-pentenoic and 5-hexenoic acid functional groups into polystyrene and demonstrated these functional groups can be used as linkers in solid phase organic synthesis. These linkers are stable to acidic, basic conditions and general reagents used in organic synthesis. Products can be released from the solid support by using mild electrophiles such as iodine and recovered with extraction



Scheme 4. Proposed mechanism of cleavage pathway for reactions performed on 2-methyl-6-(*N*-methyl-*N*-PS)-4-hexenoic acid (**12**).

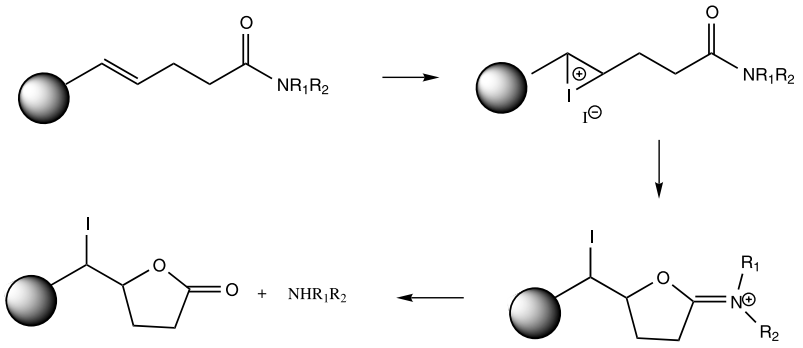
work up. The mild cleavage condition and easy work up process has an advantage, especially in combinatorial chemistry, when comparing with other linkers, such as allyl alcohol[24] and octanediol[25] functionalized resins that are using oxidants or electrophiles for cleavage and leave a residual group on the products. The optimization of synthetic conditions, characterization of the intermediate, loading of the functional group on the resin, and the scope of its application will be further investigated and the result will be reported in due course.

Acknowledgements

We would like to thank Mrs. Jun Zhao for the LC–MS, Dr. Robert Nicewonger and the referee for their valuable comments on this manuscript.

References

1. Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.
2. Seeberger, P. H.; Haase, W.-C. *Chem. Rev.* **2000**, *100*, 4349–4393.
3. Franzen, R. G. *J. Comb. Chem.* **2000**, *2*, 195–214.
4. Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91.
5. Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
6. James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946.
7. Guo, M.-J.; Varady, L. *Tetrahedron Lett.* **2002**, *43*, 3677–3680.
8. Madsen, R.; Roberts, C.; Fraser-Reid, B. *J. Org. Chem.* **1995**, *60*, 7920–7926.
9. Guo, M.-J.; Yu, D.; Iyer, R. P.; Agrawal, S. A. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2539–2544.
10. Carrington, S.; Renault, J.; Tomasi, S.; Corbel, J.-C.; Uriac, P.; Blagbrough, I. S. *J. Chem. Soc., Chem. Commun.* **1999**, 1341–1342.
11. Merrifield resin was purchased from Novabiochem, loading 1.20 mmol/g.
12. PS-Benzaldehyde was purchased from Argonaunt, loading 1.29 mmol/g. It was dried at 50°C overnight under vacuum.
13. Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492–496.
14. In a typical experiment, the ester was suspended in THF. To the suspension 40% Bu_4NOH in methanol (2 equiv.) was added and the suspension was kept under reflux for 48 h with stirring. After removing liquid and washed with THF, the resin was suspended in THF containing 10% concentrated HCl and stirred at room temperature for 1 h. Liquid was drained and resin was washed with THF. The resin was dried in vacuum at 50°C overnight.
15. The reagent is 5 equiv. to the resin's loading.
16. (3-Carboxypropyl) triphenylphosphonium bromide (**6**) was made by refluxing one equivalent 4-bromobutyric acid and triphenyl phosphine in THF for 3 days. After removing volatile, the residue was used directly.
17. The reagent is 1.5 equiv. to the resin's loading
18. *N*-Methylaminomethyl polystyrene was purchased from Novabiochem, loading 1.13 mmol/g.
19. The dealkoxycarbonylation product (**11**) was assigned in analogy to similar reaction carried out in solution phase under the same conditions, see Ref. 7.
20. The loading of these functional groups were not measured, the equivalent was based on the resin's original loading.
21. Varady, L.; Rajur, S. B.; Nicewonger, R. B.; Guo, M.-J.; Ditto, L. *J. Chromatogr. A* **2000**, *869*, 171–179.
22. A proposed mechanism is outlined as follows:



23. The structure of compound **17** was assigned based on its LC–MS, the mechanism proposed and was not confirmed by other spectra analysis. Therefore the relative positions of NHMe, OH and I are not absolutely defined.
24. Frechet, J. M. J.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492–496.
25. Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seeberger, P. H. *Org. Lett.* **1999**, *1*, 1811–1814.