Pergamon

Tetrahedron Letters 41 (2000) 6981–6984

TETRAHEDRON LETTERS

Facile cleavage of the carbamate linker of hydroxymethyl resin and its application in syntheses requiring strongly acidic conditions

Lihu Yang*

Department of Medicinal Chemistry, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Received 27 April 2000; accepted 30 June 2000

Abstract

The carbamate linker of hydroxymethyl polystyrene is cleaved by treatment with a mixture of trifluoroacetic acid and dimethylsulfide at ambient temperature. The linker, an equivalent of Cbz, is stable to a wide range of acidic, basic, and reductive conditions. Fisher indole synthesis and Pictet–Spengler cyclization on solid support, which require 70°C in acetic acid with zinc chloride and 10% TFA in dichloromethane, respectively, were successfully carried out using this linker. The facile linker cleavage strategy enables more chemistry to be performed on hydroxymethyl polystyrene resin without recourse to HF.

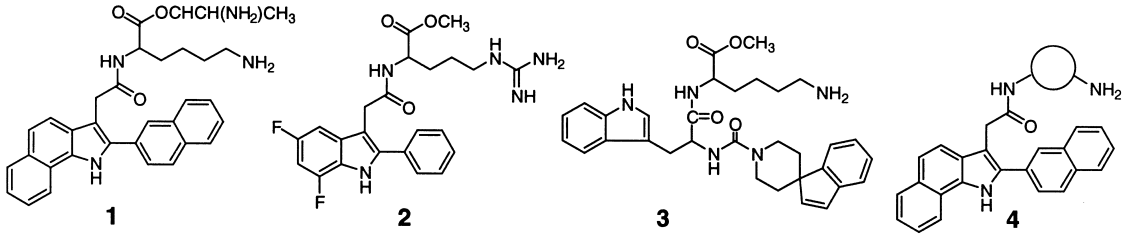
Linkers play a pivotal role in solid-phase organic synthesis. The properties of the linkers dictate the type of chemistry that can be performed on the resin-bound substrate without premature release from the resin. The most common linkers include acid-sensitive, nucleophile-labile, photocleavable and safety-catch linkers.[1,2] Although many organic reactions have been successfully carried out on solid support, great care must be taken in planning a multi-step synthesis to avoid conditions that would compromise the integrity of the linker. Ideally, a linker is stable to a variety of acidic, basic, reductive, oxidative, and even photochemical conditions, and is conveniently cleavable with common laboratory reagents. In this communication, we report the use of a carbamate linker of hydroxymethyl polystyrene in the preparation of amines. The linker, an equivalent of Cbz, is cleaved by treatment with a mixture of trifluoroacetic acid and dimethylsulfide at ambient temperature.[3] It is stable to a wide range of acidic, basic and reductive conditions.

Screening of the Merck combinatorial libraries on somatostatin receptors identified the 2-aryl indole leads **1** and **2**.[4] A close inspection revealed that the 2-aryl indole lead has structural similarity to the previously discovered peptidal mimetic somatostatin agonist **3**.[5] SAR studies in the earlier class indicated that the lysine part of the molecule plays an important part for receptor

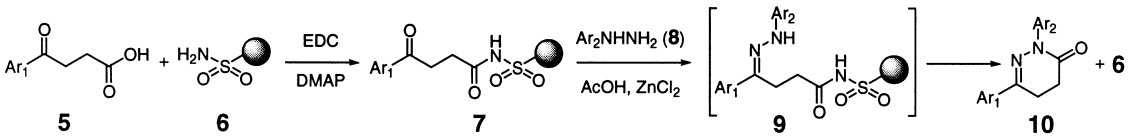
* Corresponding author. Fax: 732 594 3007; e-mail: lihu_yang@merck.com

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01192-8

affinity and subtype selectivity.[6] To rapidly study the effect of diamines in the 2-arylindole lead series, we chose to use solid-phase chemistry. A solid-phase synthesis of this class of 2-arylindoles had been described earlier.[7] A key step in the synthesis is the reaction between hydrazines and resin bound ketoacids in acetic acid at 70°C using $ZnCl_2$ as a catalyst. Such strongly acidic conditions required a robust linker/resin such as HMBA-AM resin (4-hydroxymethylbenoic acid aminomethyl resin), to which the substrate is attached via an ester. The final product can be cleaved by methanolysis in the presence of triethylamine. As a result, all the compounds prepared previously bear an ester moiety. Therefore, it is highly desirable to develop solid-phase synthesis strategies for the incorporation of different amines.



We first examined the safety-catch linker, which is stable under strong acidic conditions.[2] Once the 2-aryl indole is formed, activation and cleavage with different diamines should give the desired compounds. Coupling of the ketoacid **5** with the 4-sulfamylbutyryl AM resin **6** was achieved using EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) and stoichiometric amount of DMAP (4-dimethylaminopyridine) in dichloromethane (DCM) to give acylsufonamide **7** (Scheme 1).[8] However, exposure of the resin bound intermediate **7** to the indole formation conditions did not yield any of the desired 2-aryl indole. An intramolecular cyclization-cleavage reaction took place with **10** as the only product.[9] Clearly an alternative approach was required.

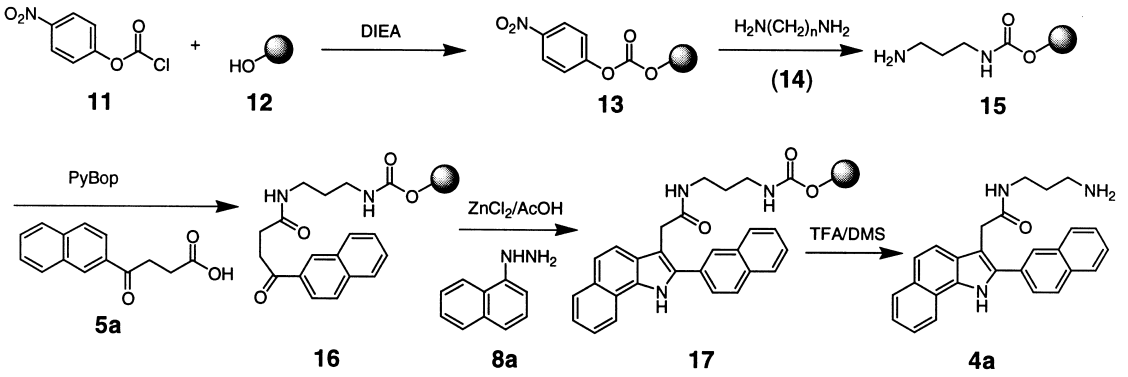


Scheme 1.

An acid-labile carbamate linker has been employed in the synthesis of a somatostatin agonist library incorporating diamines.[10] The same strategy could be adopted in this 2-aryl indole synthesis by utilising an acid stable linker. The carbamate linker from hydroxymethylpolystyrene resin has been used for the synthesis of short peptides by attaching the amino acid via the amine group.[11] The linker, an equivalent of the carboxybenzyloxy (Cbz) protecting group, is stable to acid (e.g. TFA) and is removable by HF or other strong acidic conditions. We chose to cleave the resin bound amine with TFA and dimethyl sulfide (DMS).[12]

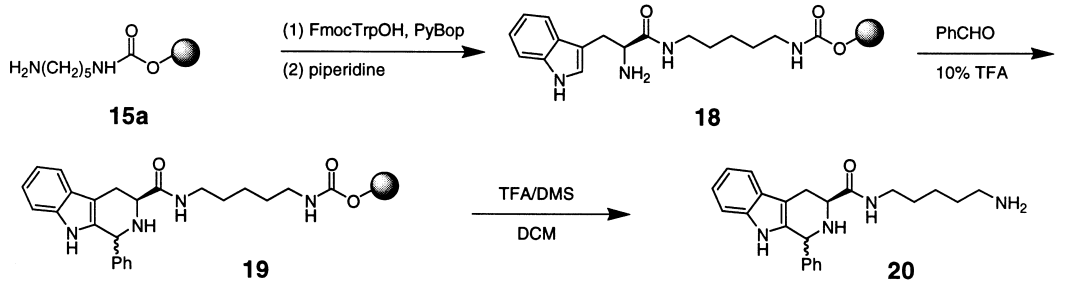
The general synthesis is shown in Scheme 2. The diamine **14** is attached to the hydroxymethylpolystyrene resin as a carbamate by reacting with the activated carbonate **13**.[13] The keto acid **5a** is then coupled to the free amine to form the amide **16** using condensation reagent PyBOP (benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate). 2-Aryl indole

formation was then carried out in 4 hours using 3 equivalents of the hydrazine hydrochloride **8a** and 1 equivalent of $ZnCl_2$ in acetic acid at 70°C. Treatment of the resin intermediate **17** with TFA and DMS (4:1) overnight at room temperature the 2-arylindole amide **4a** in good yield (60%) and high purity (95%). A number of diamines, keto acids and hydrazines were investigated with very similar results. The methology proved to be suitable for the preparation of libraries for screening as somatostatin agonists. To check the stability of this linker, intermediate **17** was subjected to a variety of basic (triethylamine, MeOH/THF, 70°C; sodium hydroxide, H_2O–MeOH/THF) and reductive (sodium borohydride, EtOH–THF) conditions. No cleavage was observed.



Scheme 2.

Similarly, we also applied the linker to the Pictet–Spengler reaction on solid support.[14] The resin bound diamine **15a** was acylated with Fmoc-Trp under the standard peptide coupling conditions, followed by Fmoc deprotection. Pictet–Spengler cyclization of **18** is carried out with benzaldehyde in 10% TFA/DCM at room temperature overnight to give **19**. The tetrahydro-β-carboline **20** is cleaved from the resin using the DMS:TFA cocktail (1:4) in 95% yield and 92% purity (Scheme 3).



Scheme 3.

In conclusion, the carbamate linker of hydroxymethyl polystyrene is cleaved by treatment with a mixture of trifluoroacetic acid and dimethylsulfide at ambient temperature. The linker, an equivalent of Cbz, is otherwise stable to acidic, basic and reductive conditions. The facile linker cleavage strategy enables more chemistry to be performed on hydroxymethyl polystyrene resin without recourse to HF.

Acknowledgements

We would like to thank Drs. Steve Hutchins, Christopher Willoughby, Kevin Chapman of Molecular Design and Diversity at Merck for helpful discussions. We are also grateful to Dr. Arthur A. Patchett for his support of this effort.

References

1. Bunin, B. A. *The Combinatorial Index*; Academic Press: San Diego, 1998.
2. (a) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636-637. (b) Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1994**, *116*, 11171–11172. (c) Backes, B. J.; Virgilio, A. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 3055–3056.
3. Yang, L.; Weber, A. E.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1993**, *34*, 7035–7038.
4. Rohrer, S. P.; Birzin, E. T.; Mosley, R. T.; Berk, S. C.; Hutchins, S. M.; Shen, D. M.; Xiong, Y.; Hayes, E. C.; Parmar, R. M.; Foor, F.; Mitra, S. W.; Degrado, S. J.; Shu, M.; Klopp, J. M.; Cai, S. J.; Blake, A.; Chan, W. W.; Pasternak, A.; Yang, L.; Patchett, A. A.; Smith, R. G.; Chapman, K. T.; Schaeffer, J. M. *Science* **1998**, *282*, 737–740.
5. Yang, L.; Berk, S. C.; Rohrer, S. P.; Mosley, R. T.; Guo, L.; Underwood, D. J.; Arison, B. H.; Birzin, E. T.; Hayes, E. C.; Mitra, S. W.; Parmar, R. M.; Cheng, K.; Wu, T. J.; Butler, B. S.; Foor, F.; Pasternak, A.; Pan, Y.; Silva, M.; Freidinger, R. M.; Smith, R. G.; Chapman, K.; Schaeffer, J. M.; Patchett, A. A. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 10836–10841.
6. Yang, L.; Guo, L.; Pasternak, A.; Mosley, R.; Rohrer, S.; Birzin, E.; Foor, F.; Cheng, K.; Schaeffer, J.; Patchett, A. A. *J. Med. Chem.* **1998**, *41*, 2175–2179.
7. Hutchins, S. M.; Chapmann, K. T. *Tetrahedron Lett.* **1996**, *37*, 4869–4872.
8. The 4-sulfamylbutyryl AM resin was purchased from Novabiochem.
9. C. Willoughby, personal communication.
10. Berk, S. C.; Rohrer, S. P.; Degrado, S. J.; Birzin, E. T.; Mosley, R. T.; Hutchins, S. M.; Pasternak, A.; Schaeffer, J. M.; Underwood, D. J.; Chapman, K. T. *J. Comb. Chem.* **1999**, *1*, 388–396.
11. (a) Lesinger, R. L.; Kornet, M. J.; Felix, A. M. *J. Am. Chem. Soc.* **1963**, *85*, 3045–3046. (b) Merrifield, R. B. *J. Am. Chem. Soc.* **1969**, *92*, 1385–1391
12. Yang, L.; Weber, A. E.; Greenlee, W. J.; Patchett, A. A. *Tetrahedron Lett.* **1993**, *34*, 7035–7038.
13. Dressman, B. A.; Spangle, L. A.; Kaldor, S. W. *Tetrahedron Lett.* **1996**, *37*, 937–940.
14. Yang, L.; Guo, L. *Tetrahedron Lett.* **1996**, *37*, 5041–5044.