Tetrahedron Letters 51 (2010) 1497–1499

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new method for cleavage of silicon–carbon linkers on glass plate supports with applications to solid-phase syntheses on silica resins

Takeshi Terauchi [a], Sachiko Machida [a], Shiro Komba [a,b,*]

[a] Biomolecular Engineering Laboratory, National Food Research Institute, 2-1-12, Kannondai, Tsukuba, Ibaraki 305-8642, Japan
[b] PRESTO, Japan Science and Technology Agency, 4-1-8, Honcho, Kawaguchi, Saitama 332-0012, Japan

ARTICLE INFO

Article history:
Received 6 October 2009
Revised 5 January 2010
Accepted 12 January 2010
Available online 18 January 2010

Keywords:
Glass substrate
Solid-phase synthesis
Cleavage of linker
Tamao–Kumada oxidation reaction

ABSTRACT

We describe herein a novel and facile method for the cleavage of a silicon-based linker on solid-phase supports such as glass plates or silica resin. The linker was efficiently cleaved by oxidation of the silicon–carbon bond (Tamao–Kumada oxidation) to release the functionalized molecule.

Recently, numerous reports concerning the research and development of solid-phase synthesis on glass substrates have appeared. Molecules immobilized on solid-phase supports have included DNA,[1] antibodies,[2] proteins,[3] peptides,[4] lectins,[5] sugar chains,[6] and other small molecules.[7] In particular, the construction technique based on a build-up approach using photolithography is widely used in industry. As methods for the detection of functional groups in immobilized molecules, a quantitative test for Fmoc-loaded resin[8] and a colorimetric test[9] have been used in polymer-supported solid-phase synthesis. Whether monitoring reactions for further elaboration or obtaining the finally constructed target product, solid-phase synthesis usually requires the cleaving of reactants from the resin matrix. To this end, many linkers and corresponding cleavage protocols have hitherto been developed and reported.[10]

However, despite the expected increase in the need and demand for build-up technology on glass substrates that will accompany the requirement for progress in biochemical analysis tools, to the best of our knowledge, no reports on the cleavage of immobilized molecules from glass substrates and their structural determination have been published to date. Hence, we initiated a study on the development of the cleavages of linkers aimed at recognizing the structures of covalently-linked molecules on glass plates. For this, we planned to examine a cleavage method that relies on the reactivity of the silicon atoms in the glass. The rationale for this was that if a silicon–carbon linkage on a glass substrate could be cleaved directly, the special structures required for cleavage of the linker systems in previous solid-phase syntheses would become unnecessary. In addition, this strategy would be more useful in that it would enable simplified preparation of the linker and prevent unanticipated cleavage of linker in any of the build-up steps because, unlike in previous strategies, the functional group to be cleaved is not introduced initially.

Previous reports on the cleavage of silicon-connected linkers on polymer beads have dealt with cleaving silicon–oxygen bonds,[11] producing alkanes (as aryl compounds), or halides by cleavage of silicon–carbon bonds through electrophilic reactions at the silicon atom with HF,[12h] TBAF,[13] CsF,[14] halogens,[15] or strong acids such as TFA.[12] While molecules can be removed with acid if they are bound as arylsilane structures, silicon–carbon bonds fixed in an SiO_2 structure are assumed to be very stable towards strongly acidic conditions. In fact, treating a modified glass plate with TFA did not result in the release of a cleavage product. HF gave a complex mixture, but did not result in an appreciable amount of the product of linker cleavage in our studies.

On the basis of these findings, we attempted to develop a new cleavage strategy using a Tamao–Kumada oxidation[16] reaction under almost neutral conditions.

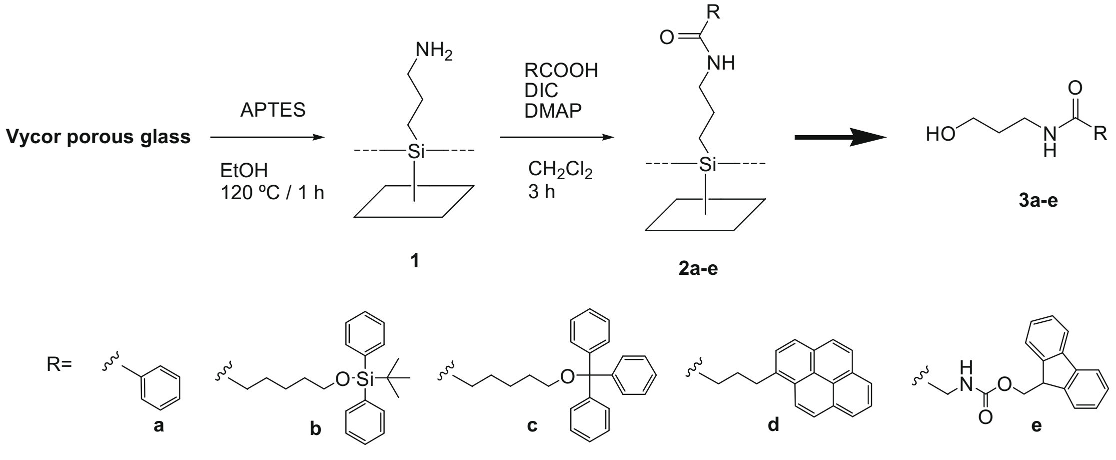
Using previously reported procedures, we first prepared aminated pore-glass (VYCOR porous glass 7930, CORNING) by treatment with (3-aminopropyl)triethoxysilane (APTES)[17] in ethanol, and then introduced several carboxylic acid moieties by condensation reactions (Scheme 1).

Before attempting to cleave the linker from the modified glasses **2a–e** by a Tamao–Kumada oxidation, we examined cleavage rates in

---

[*] Corresponding author. Tel./fax: +81 29 838 7298.
E-mail address: skomba@affrc.go.jp (S. Komba).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.01.042



Scheme 1.

the absence of any oxidants as a preliminary control. Exposure of **2a** to bases including saturated aqueous $NaHCO_3$, K_2CO_3, and 1 N NaOH, in the presence or absence of an F^- source such as KF, for 24 h resulted in the formation of a small amount of a mixture of alcohol **3a** and the corresponding trihydroxysilane. This suggested that the presence of oxygen or reactive oxygen species in solution caused partial oxidation, but in order to acquire the desired alcohol as efficiently as possible, we continued with more thorough examinations to optimize the reaction conditions with oxidants (Table 1).[18]

The use of a peroxycarboxylic acid (entries 5, 6) as an oxidant accelerated the reaction, and the reaction rates were observed to reach a plateau after 1 h. Acceleration of this reaction with increasing basicity of additives was also observed (entry 8), but rates for the cleavage of substrate **2e** bearing an Fmoc group were found to decrease (entry 23).[19]

The cleavage also occurred in the absence of fluoride ion (entry 9), and even silyl ether **3b** was released from **2b** by selective cleavage of the C–Si bond fixed in SiO_2 (entry 17). After further investigation, we found that heating (entries 12–14) accelerated the reaction to a great extent. The time course for oxidative cleavage of **2a** at 60 °C is shown in Figure 1. In the same manner, acid-labile **2c** and fluorescent **2d** were also efficiently cleaved. Thus, although the application of alkali-labile or oxidation-susceptible substrates is considered to be limited to some extent, the typical conditions for carrying out the Tamao–Kumada reaction in solution were found to be similarly applicable to cleaving the linker on glass plates.

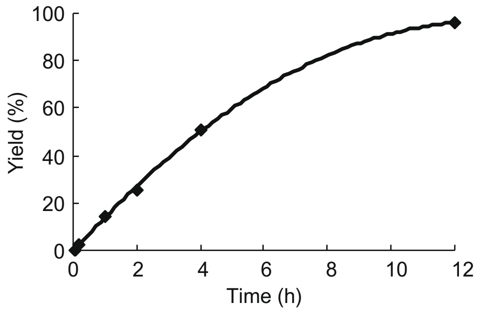


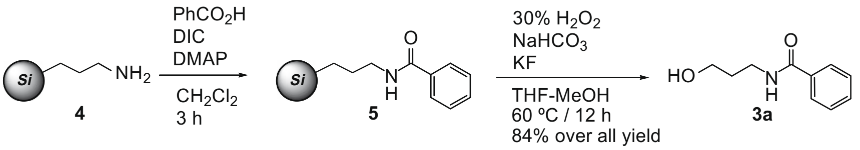
Figure 1. Time course of oxidative cleavage of **2a** at 60 °C.

Table 1
Results of oxidative cleavage of the silicon-based linkers on modified glasses **2a**–**e**

Entry	Substrate	Oxidant	Fluoride	Additive	Solvent	Temperature	Time (h)	Overall yield (%)
1	**2a**	30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	2	6[b]
2		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	4	11[b]
3		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	12	28[b]
4		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	24	35[b]
5		*m*-CPBA	KF	$NaHCO_3$	THF–MeOH	rt	1	10[b]
6		*m*-CPBA	KF	$NaHCO_3$	THF–MeOH	rt	12	13[b]
7		30% H_2O_2	KF	Na_2HPO_4	THF–MeOH	rt	24	18[b]
8		30% H_2O_2	KF	$KHCO_3$	THF–MeOH	rt	24	68[b]
9		30% H_2O_2	–	$NaHCO_3$	THF–MeOH	rt	24	32[b]
10		30% H_2O_2	KF	–	THF–MeOH	rt	24	26[b]
11		30% H_2O_2	KF	$NaHCO_3$	DMF	rt	24	46[b]
12		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	60 °C	2	25[b]
13		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	60 °C	4	51[b]
14		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	60 °C	12	96[a]
15	**2b**	30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	12	40[c]
16		30% H_2O_2	–	$NaHCO_3$	THF–MeOH	rt	12	44[c]
17		30% H_2O_2	–	$NaHCO_3$	THF–MeOH	60 °C	12	71[a]
18	**2c**	30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	60 °C	12	92[a]
19	**2d**	30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	60 °C	12	73[a]
20	**2e**	30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	2	25[d]
21		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	rt	22	45[a]
22		30% H_2O_2	KF	$NaHCO_3$	THF–MeOH	60 °C	2	7[d]
23		30% H_2O_2	KF	$KHCO_3$	THF–MeOH	rt	22	18[d]

[a] Isolated yields based on the loading determined by the Fmoc release UV assay.[8]

[b–d] Yields were calculated from the ratio of analytical HPLC integration values based on the corresponding isolated yields of entries 14, 17, and 21, respectively.



Scheme 2.

We next attempted to apply this method for solid-phase synthesis in the case of silica resin (Scheme 2). Commercially available 3-aminopropyl-functionalized silica gel **4** (Sigma–Aldrich, *si*-amine, loading: 1.08 mmol/g) was treated with benzoic acid, as in the preparation of **2a**, to produce benzamide **5**. Finally, the desired alcohol **3a** was obtained in 84% yield based on starting resin **4**, along with residual **5**, using the above oxidative cleavage conditions.

In conclusion, we have demonstrated that functionalized molecules connected through silicon–carbon bonds to glass plates or silica resin can be efficiently cleaved by a new method based on a Tamao–Kumada oxidation reaction. The approach described here does not require special structures to be incorporated into the linker to permit its cleavage, and the resulting terminal hydroxyl group is stable, convertible, and manageable. Thus, this approach should prove effective for applications in solid-phase syntheses.

Acknowledgments

This work was supported by the Program for the Promotion of Basic Research Activities in Innovative Bioscience (PROBRAIN) and by the Precursory Research for Embryonic Science and Technology (PRESTO) program. We thank Dr. H. Ono and his staff for NMR measurements, and Dr. M. Kameyama and her staff for ESI-FT-MS measurements. In addition, we also thank K. Yuhara for technical assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.042.

References and notes

1. (a) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767–773; (b) Pease, A. C.; Solas, D.; Sullivan, E. J.; Cronin, M. T.; Holmes, C. P.; Fodor, S. P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 5022–5026; (c) Singh-Gasson, S.; Green, R. D.; Yue, Y.; Nelson, C.; Blattner, F.; Sussman, M. R.; Cerrina, F. *Nat. Biotechnol.* **1999**, *17*, 974–978.
2. (a) Angenendt, P.; Glökler, J.; Murphy, D.; Lehrach, H.; Cahill, D. J. *Anal. Biochem.* **2002**, *309*, 253–260; (b) Angenendt, P.; Glökler, J.; Sobek, J.; Lehrach, H.; Cahill, D. J. *J. Chromatogr., A* **2003**, *1009*, 97–104.
3. (a) MacBeath, G.; Schreiber, S. L. *Science* **2000**, *289*, 1760–1763; (b) Rusmini, F.; Zhong, Z.; Feijen, J. *Biomacromolecules* **2007**, *8*, 1775–1789.
4. (a) Falsey, J. R.; Renil, M.; Park, S.; Li, S.; Lam, K. S. *Bioconjugate Chem.* **2001**, *12*, 346–353; (b) Panicker, R. C.; Huang, X.; Yao, S. Q. *Comb. Chem. High Throughput Screening* **2004**, *7*, 547–556. see also Ref. 1a.
5. (a) Hsu, K.-L.; Pilobello, K. T.; Mahal, L. K. *Nat. Chem. Biol.* **2006**, *2*, 153–157; (b) Lee, M.-r.; Park, S.; Shin, I. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5132–5135.
6. (a) Park, S.; Lee, M.-r.; Shin, I. *Chem. Commun.* **2008**, 4389–4399; (b) Horlacher, T.; Seeberger, P. H. *Chem. Soc. Rev.* **2008**, *37*, 1414–1422.
7. (a) MacBeath, G.; Koehler, A. N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 7967–7968; (b) Hergenrother, P. J.; Depew, K. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 7849–7850; (c) He, X. G.; Gerona-Navarro, G.; Jaffrey, S. R. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 1–7.
8. Gude, M.; Ryf, J.; White, P. D. *Lett. Pept. Sci.* **2002**, *9*, 203–206.
9. (a) Kaiser, E.; Colescott, R. L.; Bassinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598; (b) Hancock, W. S.; Battersby, J. E. *Anal. Biochem.* **1976**, *71*, 260–264; (c) Vojkovsky, T. *Pept. Res.* **1995**, *8*, 236–237; (d) Attardi, M. E.; Porcu, G.; Taddei, M. *Tetrahedron Lett.* **2000**, *41*, 7391–7394; (e) Vázquez, J.; Albericio, F. *Tetrahedron Lett.* **2001**, *42*, 6691–6693; (f) Komba, S.; Sasaki, S.; Machida, S. *Tetrahedron Lett.* **2007**, *48*, 2075–2078.
10. For example, see: Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
11. (a) Smith, E. M. *Tetrahedron Lett.* **1999**, *40*, 3285–3288; (b) Doi, T.; Sugiki, M.; Yamada, H.; Takahashi, T.; Porco, J. A., Jr. *Tetrahedron Lett.* **1999**, *40*, 2141–2144.
12. (a) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W. *J. Org. Chem.* **1998**, *63*, 4518–4521; (b) Hone, N. D.; Davies, S. G.; Devereux, N. J.; Taylor, S. L.; Baxter, A. D. *Tetrahedron Lett.* **1998**, *39*, 897–900; (c) Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7076–7077; (d) Newlander, K. A.; Chenera, B.; Veber, D. F.; Yim, N. C. F.; Moor, M. L. *J. Org. Chem.* **1997**, *62*, 6726–6732; (e) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885–2893; (f) Schuster, M.; Lucas, N.; Blechert, S. *Chem. Commun.* **1997**, 823–824; (g) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999–12000; (h) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006–6007.
13. Woolard, F. X.; Paetsch, J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 6102–6103. see also Ref. 12a.
14. See Ref. 12g.
15. Han, Y.; Walker, S. D.; Young, R. N. *Tetrahedron Lett.* **1996**, *37*, 2703–2706. see also Ref. 12e.
16. Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694–1696; Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599–7662.
17. Commercially available aminopropylated glass slides were found to have lower loading levels than those required for our purpose, so we independently fabricated them by the aminopropylation of unmodified porous glass slides. Our protocol for this was based on the results of an examination of the immobilization conditions with a selection of materials. For an example of a similar aminoalkylation protocol, see Ref. 4a.
18. A typical procedure for the oxidative cleavage was as follows. The following were added to modified glass **2a** (438 mg of a glass plate, 12.3 μmol, amino-loading: 28.2 μmol/g): THF (877 μl), MeOH (877 μl), saturated aqueous NaHCO$_3$ (877 μl), saturated aqueous KF (877 μl), and 30% aqueous H$_2$O$_2$ (877 μl). After warming at 60 °C for 12 h, the reaction mixture was allowed to cool to room temperature and then diluted with water (10 ml). The resulting mixture was extracted with EtOAc (2 × 5 ml), and the combined organic phases were concentrated and dried in vacuo to yield a slurry (2.46 mg). The crude product was purified by reversed-phase HPLC to produce **3a** (2.12 mg, 95.5% from **1**) as a colorless oil.
19. In order to assess the stability of **3e** to the oxidative conditions, we subjected it to several oxidative or basic conditions, including those of entries 21 and 23 in Table 1, in the liquid phase. Partial Fmoc cleavage was observed in most cases; an increase in basicity or temperature-accelerated Fmoc cleavage, while the presence of KF or H$_2$O$_2$ had hardly any influence.