Pergamon

Tetrahedron Letters 40 (1999) 2105–2108

TETRAHEDRON LETTERS

Triazenes as Robust and Simple Linkers for Amines in Solid-phase Organic Synthesis[1]

Stefan Bräse,* Johannes Köbberling, Dieter Enders, Ryszard Lazny,† Mingfei Wang

Institut für Organische Chemie der Technischen Hochschule, Professor-Pirlet-Straße 1, D-52074 Aachen, Germany

Siegfried Brandtner

DDTeC GmbH, D-52222 Stolberg, Germany

Received 11 November 1998; revised 6 January 1999; accepted 13 January 1999

Abstract

A new linker strategy for the attachment of aliphatic amines has been developed. Starting from Merrifield resin, an immobilized diazonium salt was prepared in two steps. Reaction of various amines gave rise to triazenes, which in turn were cleaved off upon treatment with mild acids. The triazenes have been proven to be base stable and were used in various types of transformations. The overall process is high-yielding and efficient.

Keywords: Solid-phase synthesis, Amines, Protecting groups, Triazenes

Over the last couple of years solid-phase organic synthesis (SPOS) has become one of the major tools in combinatorial chemistry, since it allows the rapid assembly of small molecule libraries [2–8]. The latter have been extensively used for the high-throughput-screening [9,10]. The advantage of the SPOS relies on the ease of purification processes during the synthesis and its preference for automated handling.

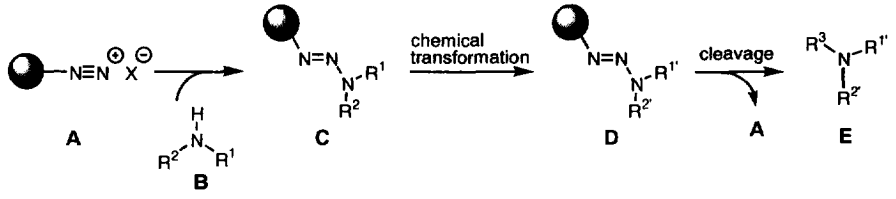
For the application of processes used in SPOS miscellaneous linker types for amines have been developed [11–34], which resist various reaction conditions. We have already demonstrated the use of triazenes as linker moieties in SPOS to attach arenes in a traceless manner [35] and the use of triazenes as protecting groups for sensitive amines [36]. Herein the approach for a reversed strategy to link amines is presented.

* Telefax: Int. + (49) (0) 241/8888127; E-mail: Braese@oc.RWTH-Aachen.de

† New address: Institute of Chemistry, University of Bialystok, Al. Pilsudskiego 11/4, 15-443 Bialystok, Poland

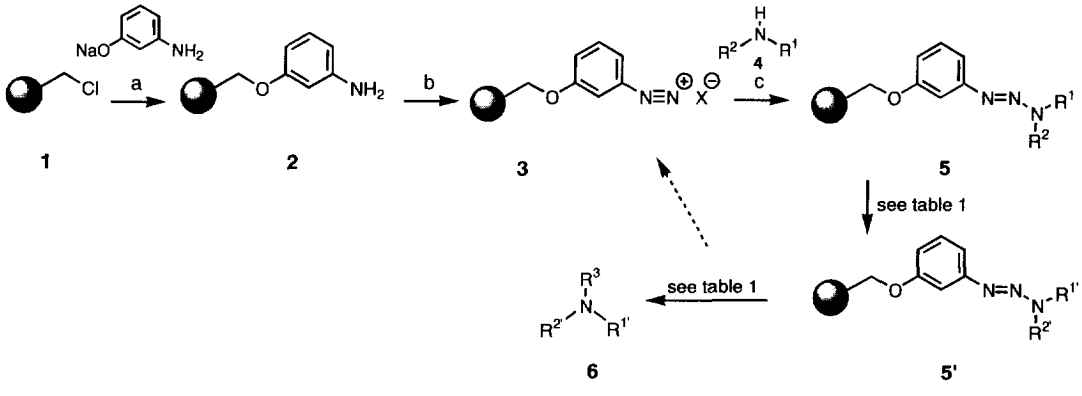
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00160-4

The strategy is described as follows. Starting from an immobilized diazonium salt **A** on a resin, reaction with amines **B** results in the formation of triazenes **C**. Chemical modification of the resin bound amine yields resin **D**. Cleavage of the N-N single bond, affected by electrophiles, should give rise to the regeneration of the diazonium resin **A** and modified amine **E** (Scheme 1).



Scheme 1. Strategy for a triazene linker.

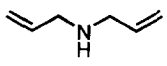
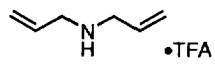
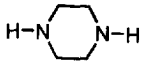
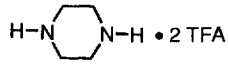
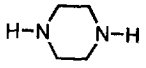
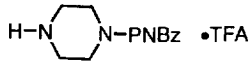
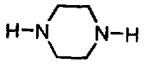
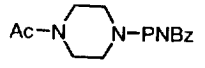
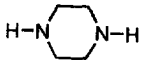
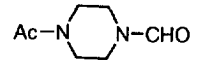
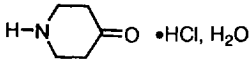
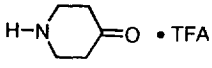
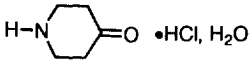
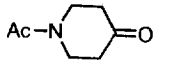
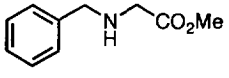
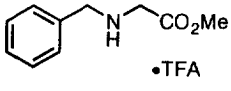
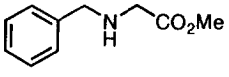
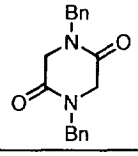
To prove this hypothesis, Merrifield resin (**1**) (chloromethylated polystyrene, 1% cross-linked (divinylbenzene), 0.72–1.2 mmol/g) was treated with deprotonated *m*-hydroxyaniline [37] (NaH in DMF) to give the resin **2** in high yield [38]. Treatment of **2** with *t*BuONO in the presence of trifluoroborane-etherate in THF at −10 °C resulted in the formation of the resin salt **3**. The wet product is reasonable stable and was treated, after being washed, with various amines **4** (Table 1) in dichloromethane at −10 °C to room temperature to give the triazenes **5**. The aniline and triazene resins **2** and **5**, are stable for weeks at room temperature (Scheme 2). Piperazines attached to the resin were modified by acylation in presence of triethylamine or converted to the corresponding formamide using methyl formate.



Scheme 2. Synthesis and use of the triazene linker. a) DMF, 60 °C, 48 h. b) *t*BuONO, $Et_2O{\bullet}BF_3$, −10 °C, THF, 2 h. c) Amine, NEt_3 (see Table 1).

Cleavage was achieved by treatment with 10% trifluoroacetic acid in dichloromethane (Table 1) to give the desired products **6** in excellent overall yield and purity (in general over 90%). The resin can be regenerated, if the cleavage is conducted with tetrafluoroboronic acid.

Table 1. Attachment, modification and cleavage of amines prepared.

Amine **4**	Amine **6**	Conditions		
		A		C
		A		C
		A	D	C
		A	D	E
		A	F	E
		B		C
		B		E
		A		C
		A	G	H

A: 1. resin **2**, *t*BuONO, $Et_2O{\bullet}BF_3$, THF, −10 °C; 2. **4**, 1h → RT. **B**: 1. resin **2**, *t*BuONO, $Et_2O{\bullet}BF_3$, THF, −10 °C; 2. TEA, **4**, 1h → room temp.. **C**: 10% TFA in CH_2Cl_2, 5 min, room temp. **D**: PNBzCl, NEt_3, THF, room temp. 24 h. **E**: AcCl, THF, room temp., 12 h **F**: HCO_2Me, room temp. 2 d. **G**: 1. LiOH, H_2O_2, 0 °C; 2. N-BnGlyOMe, BOP-Cl. **H**: 50% TFA in CH_2Cl_2, room temp., 10 h. PNBz = *para*-nitrobenzoyl.

Furthermore, cleavage with acetyl chloride with exclusion of triethylamine gave rise to the formation of *N*,*N*-dialkylacetamides **6** (R^3 = COMe) (Table 1).

Under these conditions even sensitive amines, such as 4-piperidone, can be successfully attached to solid support. Preliminary results indicate that the use of this linker system can be extended towards immobilizing primary amines, too. These can be acylated yielding a backbone amide linker (BAL) system [39].

In conclusion, a new linker for aliphatic amines on solid support has been developed on a triazene basis. The synthesis of the resin has been achieved in two steps starting from Merrifield resin. Since various kinds of chemical transformations have been shown to be compatible with the triazene linkage [35,36], this new triazene solid-phase handle can be used in many applications.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft (Leibniz price to D. E., Sonderforschungsbereich 380, Transferbereich 11) and the Fonds der Chemischen Industrie (Liebig stipend to St. B.). We thank the companies BASF AG, Bayer AG and Grünenthal GmbH for donations of chemicals.

References

[1] Part 3 in the series: Nitrogen-based linker. A part of this work has been presented at Schliersee conference, October 1998. For part 1, see ref. [35]. For part 2, see ref. [36].
[2] Gordon EM, Barrett RW, Dower WJ, Fodor SPA, Gallop MA. J. Med. Chem. 1994;37:1385-1401.
[3] Ellman J. Acc. Chem. Res. 1996;29:132-143.
[4] Armstrong RW, Combs AP, Tempest PA, Brown SD, Keating TA. Acc. Chem. Res. 1996;29: 123-131.
[5] Balkenhohl F, von dem Bussche-Hünnefeld C, Lansky A, Zechel C. Angew. Chem. Int. Ed. Engl. 1996;35:2289-2337.
[6] Früchtel, JS, Jung G. In G. Jung (Ed.) 1996, Combinatorial Peptide and Nonpeptide Libraries: A Handbook. (pp. 19-78). VCH, Weinheim, Germany.
[7] Hermkens PHH, Ottenheijm HCJ, Rees D. Tetrahedron 1996;52:4527-4554.
[8] Kyle DJ. Drug Disc. Today 1997;2:229-234.
[9] Wallace RW. Drug Disc. Today 1997;2:355-355.
[10] Burbaum JJ, Sigal NH. Curr. Opin. Chem. Biol. 1997;1:72-78.
[11] Meisenbach M, Voelter W. Chem. Lett 1997:1265-1266.
[12] Alsina J, Rabanal F, Giralt E, Albericio F. Tetrahedron Lett 1994;35, 9633-9636.
[13] Bannwarth W, J. H, Barner R. Bioorg. Med. Chem. Lett. 1996,;6: 1525-1528.
[14] Dressman BA, Spangle LA, Kaldor SW. Tetrahedron Lett. 1996;37:937-940.
[15] Kaljuste K, Unden A. Tetrahedron Lett 1996;35:3031-3034.
[16] Gouilleux L, Fehrentz JA, Winternitz F, Martinez J. Tetrahedron Lett. 1996;37:7031-7034.
[17] Boojamra CG, Burow KM, Thompson LA, Ellman JA. J. Org. Chem. 1997;62,:1240-1256.
[18] Brown AR, Rees DC, Rankovic Z, Morphy JR. J. Am. Chem. Soc. 1997;119,:3288-3295.
[19] Hernandez AS, Hodges JC. J. Org. Chem. 1997;38:4861-4864.
[20] Ngu K, Patel DV. Tetrahedron Lett. 1997;38:973-976.
[21] Ho CY, Kukla MJ. Tetrahedron Lett. 1997;38:2799-2802.
[22] Furth PS, Reitman MS, Cook AF. Tetrahedron Lett. 1997;38:5403-5406.
[23] Swayze EE. Tetrahedron Lett. 1997;38:8465-8468.
[24] Conti P, Demont D, Cals J, Ottenheijm HCJ, Leysen D. Tetrahedron Lett. 1997;38:2915-2918.
[25] Kay C, Murray PJ, Sandow L, Holmes AB. Tetrahedron Lett. 1997;39:6941-6944.
[26] Hird NW, Irie K, Nagai K. Tetrahedron Lett. 1997;38:7111-7114.
[27] Fitzpatrick LJ, Rivero RA. Tetrahedron Lett. 1997;38:7479-7482.
[28] Hsieh H, Wu Y, Chen S, Wang K. Chem. Commun. 1998:649-650.
[29] Dressman B, Singh U, Kaldor S. Tetrahedron Lett. 1998;39:3631-3634.
[30] Lorsbach BK, Bagdanoff JT, Miller RB, Kurth MJ. J. Org. Chem. 1998;63:2244-2250.
[31] Estep KG, Neipp CE, Stramiello LMS, Adam MD, Allen MP, Robinson S, Roskamp EJ. J. Org. Chem. 1998;63:5300-5301.
[32] Breitenbucher JG, Johnson CR, Haight M, Phelan JC. Tetrahedron Lett. 1998;39:1295-1298.
[33] Del Fresno M, Alsina J, Royo M, Barany G, Albericio F. Tetrahedron Lett. 1998;39:2639-2642.
[34] Chhabra S, Khan A, Bycroft B. Tetrahedron Lett 1998;39:3585-3588.
[35] Bräse S, Enders D, Köbberling J, Avemaria F. Angew. Chem. Int. Ed. Engl. 1998;37:3413-3415.
[36] Bräse S, Köbberling J, Enders D, Lazny R, Poplawski J. Synlett, submitted.
[37] *m*-Hydroxyaniline is more stable towards alkaline solution than the *ortho* and *para* derivative.
[38] The yields are based on the elemental analysis of the product resin. All new non-polymeric compounds have been characterized by NMR, MS, IR and elemental analysis or HRMS, respectively. The resins have been characterized by elemental analysis and IR.
[39] Bräse S, Dahmen S. Unpublished results.