Pergamon

Tetrahedron Letters 43 (2002) 1587–1589

TETRAHEDRON LETTERS

Convenient synthesis of disulfide substrates for trypanothione reductase using polymer-supported reagents

Kelly Chibale,[a,*] Alex Chipeleme[a] and Stuart Warren[b]

[a]*Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa*
[b]*Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, UK*

Received 6 November 2001; accepted 4 January 2002

Abstract—Operationally simplified and high yielding methods for the preparation of *N*,*N*′-bis(benzyloxycarbonyl)-1-L-cysteinylglycyl-3-dimethylaminopropylamide disulfide, an alternative substrate for trypanothione reductase, and a structural analogue, using polymer-supported reagents are described. © 2002 Elsevier Science Ltd. All rights reserved.

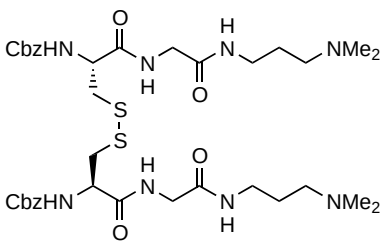
N,*N*′ - Bis(benzyloxycarbonyl) - 1 - L - cysteinylglycyl - 3-dimethylaminopropylamide disulfide **1** is a known alternative synthetic substrate for the anti-oxidative enzyme trypanothione reductase (TryR).[1] Unlike the natural substrate trypanothione disulfide **2**, compound **1** has been used as a basis for non-reducible inhibitors of TryR.[2] Compound **1** has been synthesised, in 46% overall yield, using solution phase chemistry.[1] In spite of the few steps involved in the reported synthesis of **1**, the isolation and purification of the products required laborious and time-consuming chromatography.

In this letter we report operationally simplified and high yielding methods for the synthesis of **1** and its analogue **3** using polymer-supported reagents, 2% crosslinked polystyrene beads containing di-imide residues **4**,[3] macroporous polystyrene anion-exchange beads containing quaternary ammonium salt moieties **5** in the carbonate form[4] and 2% crosslinked polystyrene beads containing *N*,*N*-dialkylaminopyridine residues **6**.[5]

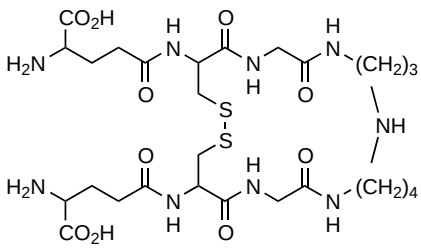
The synthesis of **1** was executed as depicted in Scheme 1.

The starting point for the synthesis of **1** was the coupling reaction of **7** (prepared from glycine and benzyl chloroformate) and 3-*N*,*N*-dimethylaminopropylamine according to the literature procedure.[3] Activation of the carboxyl group of **7** by P-EDC **4** in the presence of 3-*N*,*N*-dimethylaminopropylamine gave **8** in high yield after filtration. Removal of the benzyloxycarbonyl (Cbz) group by catalytic hydrogenation gave **9** in quantitative yield after filtration. Coupling of **9** and cystine derivative **10** in the presence of **4** and 1-hydroxybenzotriazole (HOBT), followed by removal of HOBT using **5** as a scavenger[6] and filtration gave **1** in 72% overall yield.[7]

A similar strategy was employed for the synthesis of analogue **3** (Scheme 2). The starting point was the preparation of **12** using the coupling conditions



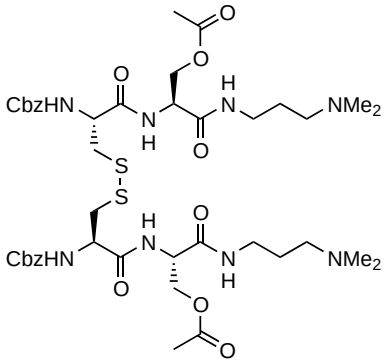
1



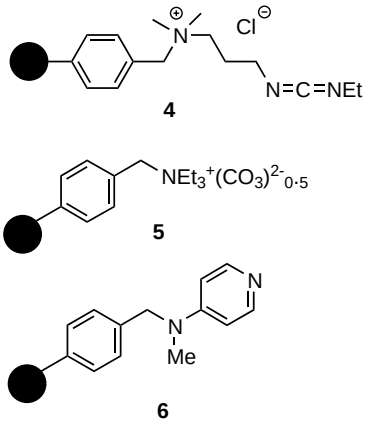
2

* Corresponding author. Fax: +27 21 689 7499; e-mail: chibale@science.uct.ac.za

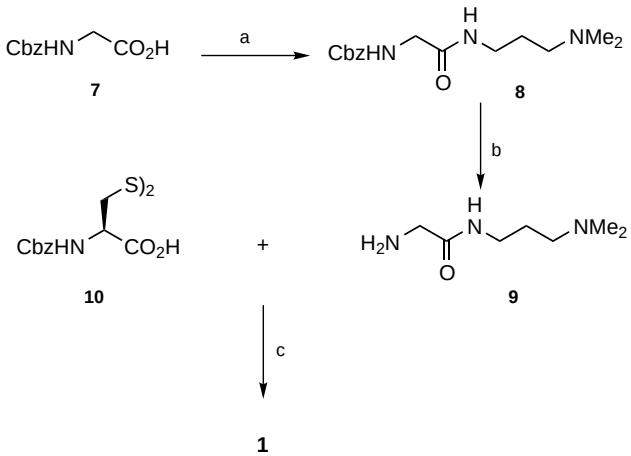
PII: S0040-4039(02)00064-3



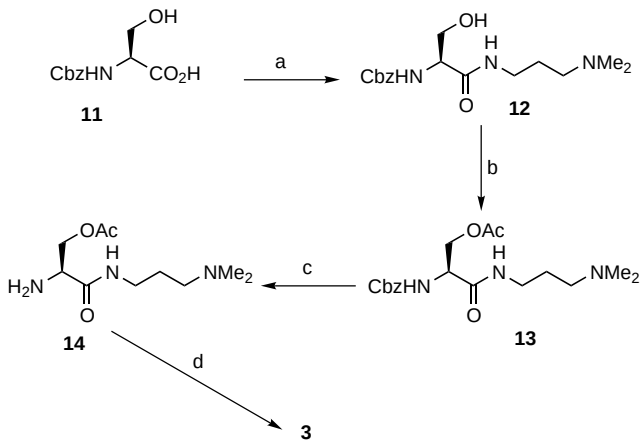
3



4 5 6



Scheme 1. *Reagents and conditions*: (a) 2.5 equiv. of **4**, 1.0 equiv. of $H_2N(CH_2)_3N(CH_3)_2$, $CHCl_3$, 25°C, 16 h, filtration, 91%; (b) 10% Pd/C, H_2, MeOH, 25°C, 2 h, filtration, 100%; (c) 2.5 equiv. of **4**, 1.0 equiv. of HOBT, $CHCl_3$, 25°C, 16 h, then 3.0 equiv. of **5**, CH_2Cl_2, 25°C, 3 h, filtration, 79%.



Scheme 2. *Reagents and conditions*: (a) 2.5 equiv. of **4**, 1.0 equiv. of $H_2N(CH_2)_3N(CH_3)_2$, 1.0 equiv. of HOBT, $CHCl_3$, 25°C, 16 h and then 3.0 equiv. of **5**, CH_2Cl_2, 25°C, 3 h, filtration, 96%; (b) 2.0 equiv. of AcCl, 4.0 equiv. of **6**, CH_2Cl_2, 25°C, 12 h, filtration, 97%; (c) 10% Pd/C, H_2, MeOH, 25°C, 2 h, filtration, 100%; (d) 2.5 equiv. of **4**, 2.0 equiv. of **10**, 1.0 equiv. of HOBT, $CHCl_3$, 25°C, 16 h and then 3.0 equiv. of **5**, CH_2Cl_2, 25°C, 3 h, filtration, 74%.

employed in the last two steps for the synthesis of **1**. Compound **12** was treated with acetyl chloride in the presence of the acylation catalyst **6** to furnish **13**, which was subjected to catalytic hydrogenation to afford **14** in quantitative yield after filtration. In a similar fashion **14** was coupled with cystine derivative **10** to give **3** in 69% overall yield.[7]

In conclusion our strategy for the synthesis of **1** and its analogue **3** using polymer-supported reagents proved to be superior in terms of simplicity, efficiency and yields in comparison to the reported solution phase synthesis.[1] Coupled with the reported solid-phase syntheses of the natural substrate,[8–10] our approach to the synthesis of **1** should provide options for synthesising these disulfides and related compounds.

General procedure for amide bond formation and removal of HOBT. To a suspension of **4** [1.0 mmol of chloromethylated poly(styrene-co-divinyl benzene), 2% crosslinked, 1.4 mmol/g loading capacity] in chloroform (10 ml), the acid (0.44 mmol) and amine (0.4 mmol) were added. The reaction mixture was shaken for 24 h at room temperature and then filtered. The resin was washed with chloroform (3×5 ml) and the combined filtrate was concentrated under reduced pressure. The residue was re-dissolved in dichloromethane and then **5** [0.88 mmol of macroporous poly(styrene-co-divinyl benzene), anion-exchange resin, 2.64 mmol/g loading capacity] was added. The resultant mixture was shaken at room temperature for 2 h, filtered, washed with dichloromethane (3×5 ml) and concentrated to give the product.

Acknowledgements

Financial support from the Wellcome Trust (grant no. 052075/Z/97/Z/JMW/JPS/CG) is gratefully acknowledged.

References

1. El-Waer, A.; Douglas, K. T.; Smith, K.; Fairlamb, A. H. *Anal. Biochem.* **1991**, *198*, 212–216.

2. Tromelin, A.; Moutiez, M.; Meziane-Cherif, D.; Aumercier, M.; Tartar, M.; Sergheraert, C. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1971–1976.
3. Desai, M. C.; Stramiello, L. M. *Tetrahedron Lett.* **1993**, *34*, 7685–7688.
4. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Synthesis* **1981**, 793–798.
5. Shinkai, S.; Tsuji, H.; Hara, Y.; Manabe, O. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 631–632.
6. Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, *38*, 7959–7962.
7. Compound **1**: δ_H (300 MHz; $CDCl_3$) 1.62 (4H, quint. *J* 6.6, 2×$^2CH_2$), 2.22 (12H, s, NMe_2), 2.32 (4H, t, *J* 6.6, 2×$^3CH_2$), 3.02 (4H, m, 2×$C_\beta H_2$, 2×Cys), 3.30 (4H, m, 2×$^1CH_2$), 3.87 (4H, m, 2×$C_\alpha H_2$, 2×Gly), 4.80 (2H, m, 2×$C_\alpha H$, 2×Cys), 5.12 (4H, s, CH_2Ph), 6.15 (2H, d, *J* 8.4, 2×Cys), 7.33 (10H, m, *Ph*), 7.40 (2H, br s, 2×Gly), 7.90 (2H, br s, 2×OCO*NH*CH); δ_c (75 MHz, $CDCl_3$) 26.1, 39.5, 43.4, 44.0, 45.2, 54.6, 58.0, 63.0, 67.3, 128.1, 128.2, 128.5, 136.1, 168.2, 170.5.
Compound **3**: δ_H (300 MHz; $CDCl_3$) 1.62 (4H, quint. *J* 6.9, 2×$^2CH_2$), 2.00 (6H, s, CH_3CO) 2.66 (12H, s, NMe_2), 2.95 (4H, m, 2×$^1CH_2$), 3.02 (4H, m, 2×$^3CH_2$), 3.32 (4H, m, 2×$C_\beta H_2$, 2×Cys), 3.70 (2H, dd, *J* 6.9 and 3.9, 2×$C_\alpha H$, 2×Cys), 3.97 (2H, m, 2×$C_\alpha H$, 2×Ser), 4.43 (4H, m, 2×$C_\beta H_2$, 2×Ser), 5.12 (4H, s, CH_2Ph), 6.15 (2H, br s, 2×Cys), 7.33 (10H, m, *Ph*), 7.50 (2H, d, *J* 7.8, 2×Ser), 7.90 (2H, br t, *J* 5.7, 2×CHCO*NH*). δ_c (75 MHz, $CDCl_3$) 23.1, 24.4, 35.0, 40.0, 42.9, 55.0, 55.8, 62.7, 66.6, 69.0, 128.0, 128.2, 128.5, 141.0, 156.0, 170.1, 171.8.
8. Marsh, I. R.; Bradley, M. *Tetrahedron* **1997**, *51*, 17317–17334.
9. Kellam, B.; Bycroft, B. W.; Chhabra, S. R. *Tetrahedron Lett.* **1997**, *38*, 4849–4852.
10. Fauchet, V.; Bourel, L.; Tartar, A.; Sergheraert, C. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2559–2562.