Tetrahedron Letters 49 (2008) 6308–6310

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Selective monoprotection of 1,4,7,10-tetraazacyclododecane via direct reaction with 4-nitrophenyl active esters

Anna M. Skwierawska *

Gdańsk University of Technology, Narutowicza 11/12, Gdańsk 80-952, Poland

ARTICLE INFO

Article history:
Received 17 June 2008
Revised 11 August 2008
Accepted 18 August 2008
Available online 22 August 2008

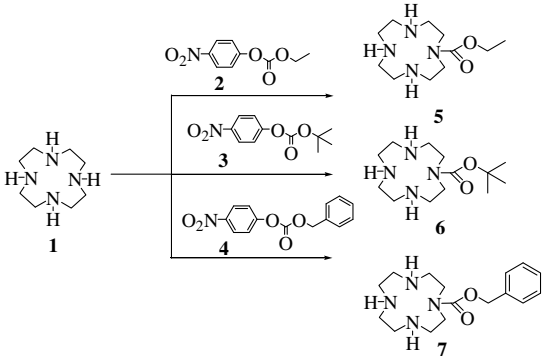
Keywords:
Cyclen
Active esters
Monoprotection

ABSTRACT

A simple, one-pot preparation of monoprotected 1,4,7,10-tetraazacyclododecanes via an efficient acylation reaction with 4-nitrophenyl active esters has been developed.

One of the most important ligands in medical inorganic chemistry is 1,4,7,10-tetraazacyclododecane (cyclen). Derivatives of this macrocycle are used to form stable metal complexes with gadolinium, copper, indium, gallium, zinc, and other metals. These complexes are used extensively in the fields of medical imaging and radiotherapy.[1] To utilize these compounds in medicine, derivatization of cyclen is required in order to impart specific physical properties and to assemble specific biological requirements, such as recognition of a particular organ or receptor. Regioselective substitution of the four nitrogen atoms of cyclen is a crucial step for synthesis of a new cyclen-based radiometal complexes and bifunctional chelating reagents. For instance, introduction of three chelating groups, such as acetic acid, phosphonic acid, or monoesters of phosphonic acid onto the nitrogen atoms has a huge effect on the coordination geometry and formal charge under physiological conditions, effecting both the thermodynamic stability and kinetic inertness.[2] Additional cyclen modification by substitution of a hydrophobic, chromogenic, or luminescent group makes the molecule more specific and sensitive in molecular recognition. DO3A (three acetates), DOTA (four acetates), and DO3P (three methylene phosphonic acids) and their derivatives with a hydrophobic or luminescent group are extensively used cyclen-based compounds for medical purposes.[3]

There are two main options for the synthesis of these bifunctional compounds. N-Monoalkylation has been effected by the use of an excess of cyclen relative to electrophiles.[4] This methodology is undesirable for less accessible or expensive electrophiles. With highly sterically hindered alkylating agents, selective N-monosubstitution has been effected using equimolar amounts of reactants.[5] Alternative methods reported for N-monoalkylation include triprotection of cyclen as boron,[6] phosphorus,[7] group VI metal carbonyl,[8] silicon derivatives,[9] 1,1-dimethoxy-*N*,*N*-dimethylmethylamine,[10] Ts,[11] or Boc[12] followed by conversion of these intermediates to monoprotected cyclen compounds. In these methods, the overall yield of monoprotection based on cyclen is in the range of 25–50% owing to the low yields of the protection steps and the requisite chromatographic purification of cyclen products. There is also a method in which three of the four nitrogen atoms of cyclen were protected as formyl groups by reaction with four equivalents of chloral hydrate in ethanol.[13] The product was further reacted with an excess of benzyl chloroformate to give pure



Scheme 1. Reagents and conditions: 1 mmol of 1,4,7,10-tetraazacyclododecane, 1 mmol of 4-nitrophenyl active ester, 20 mL dichloromethane, room temperature, 12 h.

* Tel.: +48 58 347 2288; fax: +48 58 347 1949.
E-mail address: skwieraw@chem.pg.gda.pl.

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.059

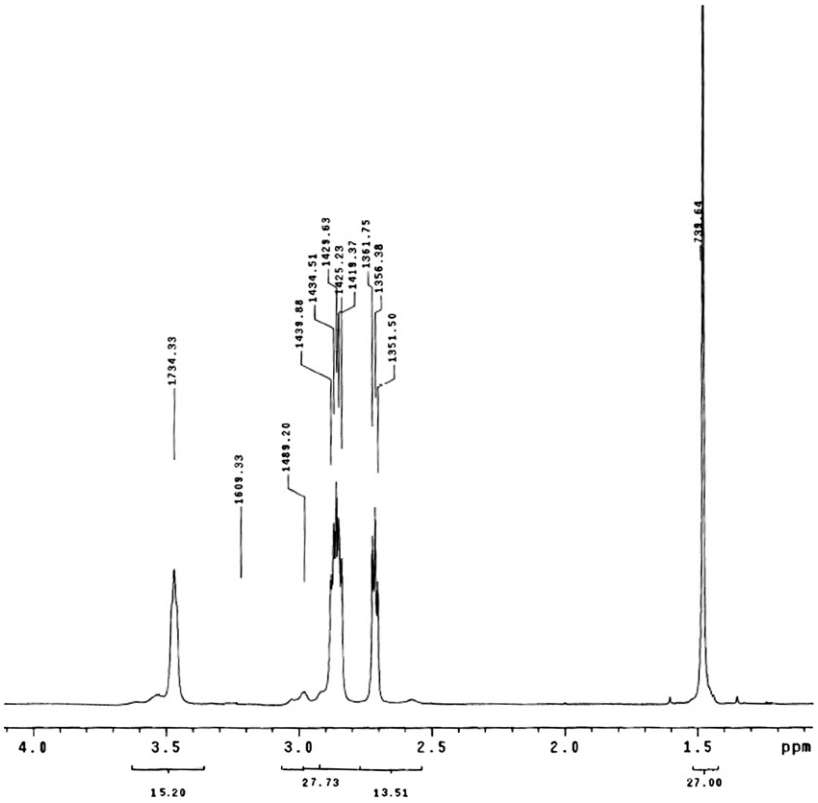


Figure 1. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 1-*tert*-butoxycarbonyl-1,4,7,10-tetraazacyclododecane **6**.

1-benzyloxycarbonyl-4,7,10-triformyl-1,4,7,10-tetraazacyclododecane in almost quantitative yield. Mild acidic treatment (1 M HCl, 50 °C) led to selective cleavage of the three formyl groups without attacking the Cbz group. Elevated temperature and higher acidity would cleave the Cbz–N bond to return to the starting cyclen itself.

For comparison, we present a method which allows direct introduction of one ethoxycarbonyl, Boc, or Cbz group in a one-pot acylation reaction under very mild conditions. An appropriate 4-nitrophenyl active ester[14] is dissolved in dichloromethane and a stoichiometric amount of cyclen is added (Scheme 1).

The reaction mixture was stirred at room temperature for 12 h. Simple column purification gave the products in yields of 70–80%. Noteworthy is the fact that tetra, tri, and disubstituted products were formed in only trace quantities and were not isolated.

Two others solvents, THF and chloroform, were tested. The yields of monoprotected products were 30–40% in the case of THF, and 40–50% in chloroform.

All the compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and high resolution mass spectroscopy. Due to the hindered rotation of the carbamate group, the signals in the ^{1}H NMR spectrum of the diprotected compounds are broad.[15,16] Monoprotected derivatives of cyclen give much simpler spectra (Figs. 1–3).

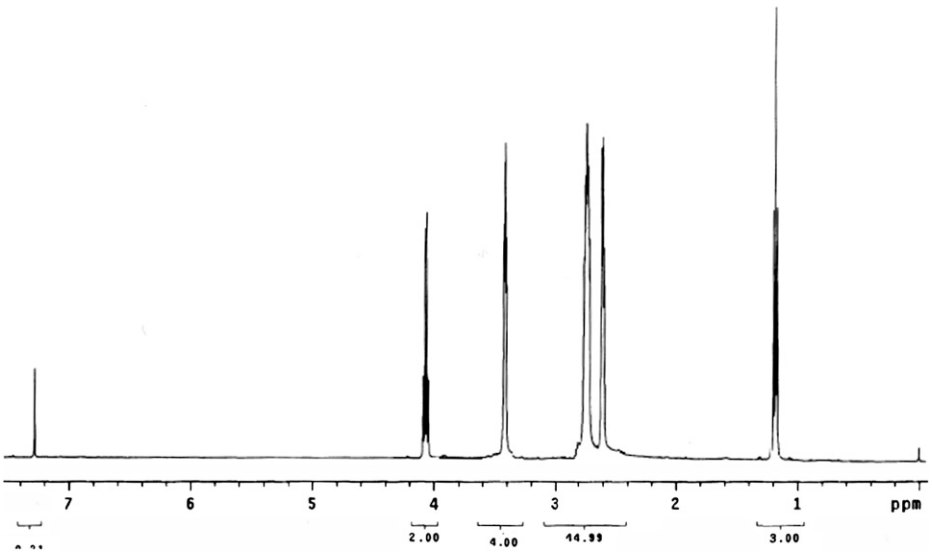


Figure 2. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 1-ethoxycarbonyl-1,4,7,10-tetraazacyclododecane **5**.

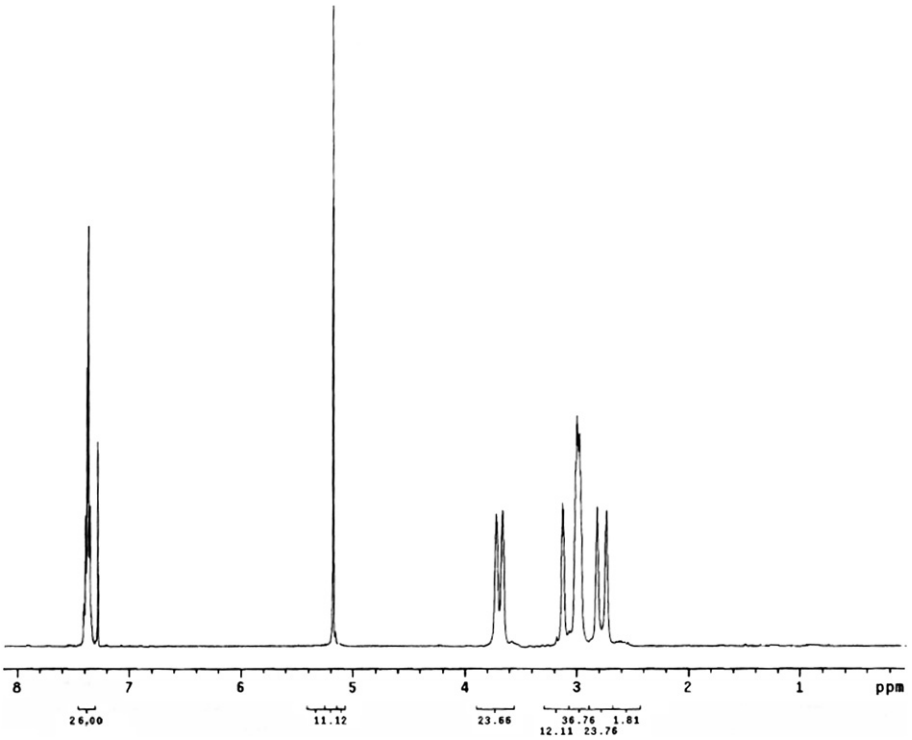


Figure 3. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of 1-benzyloxycarbonyl-1,4,7,10-tetraazacyclododecane **7**.

Preliminary experiments indicated that the ethoxycarbonyl derivative is difficult to cleave, in agreement with the literature reports.[17] It proved to be quite resistant to acid or base hydrolysis. However, the Boc group was easy to cleave using TFA in dichloromethane solution or HCl in ether solution. Pure 1,4,7,10-tetraazacyclododecane was obtained as the cyclen 4TFA salt in quantitative yield after 20 min.

The benzyloxycarbonyl group has advantages as a protecting group for nitrogen atoms because it can be easily removed by catalytic hydrogenation in addition to acidic hydrolysis. We applied cyclohexene as a hydrogen donor and 10% Pd/C as catalyst. The mixture was refluxed in ethanol for 1 h. The catalyst was filtered off and the solvent was removed under reduced pressure. This procedure produced the corresponding pure cyclen in quantitative yield.

In conclusion, three mono-N-protected cyclen compounds were successfully prepared in high yields without time-consuming supporting derivatization reactions.[18] Cleavage of Boc and Cbz groups was selective and rapid. Mono-*N*-Cbz-cyclen and mono-*N*-Boc-cyclen could be used as synthons for the preparation of a variety of bifunctional 1,4,7,10-tetraazacyclododecane derivatives.

Acknowledgment

This work was supported by BW014694/054.

References and notes

1. Anderson, C. J.; Welch, M. J. *Chem. Rev.* **1999**, *99*, 2219; Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293.
2. Bianchi, A.; Calabi, L.; Giorgi, C.; Losi, P.; Mariani, P.; Palano, D.; Paoli, P.; Rossi, P.; Valtancoli, B. *J. Chem. Soc., Dalton Trans.* **2001**, 917.
3. Liang, X.; Parkinson, J. A.; Weishaeupl, M.; Gould, R. O.; Paisey, S. J.; Park, H. S.; Hunter, T. M.; Blindauer, C. A.; Parsons, S.; Sadler, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 9105.
4. Li, C.; Wong, W.-T. *Tetrahedron Lett.* **2002**, *43*, 3217.
5. Kruper, W. J., Jr.; Langhoff, P. R. C. A. *J. Org. Chem.* **1993**, *58*, 3869.
6. Bernard, H.; Yaouanc, J. J.; Clement, J. C.; Des Abbayes, H.; Handel, H. *Tetrahedron Lett.* **1991**, *32*, 639.
7. Filali, A.; Yaouanc, J. J.; Handel, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 560.
8. Yaouanc, J. J.; Le Gall, N.; Clement, J. C.; Handel, H.; Des Abbayes, H. *Tetrahedron Lett.* **1995**, *1*, 79.
9. Roignant, A.; Gardinier, I.; Bernard, H.; Yaouanc, J. J.; Handel, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1233.
10. Li, Z.; Undheim, K. *Acta Chim. Scand.* **1998**, *52*, 1247.
11. Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265.
12. Denat, F.; Brandes, S.; Guilard, R. *Synlett* **2000**, 561.
13. Yoo, J.; Reichert, D. E.; Welch, M. J. *Chem. Commun.* **2003**, 766.
14. Rahmathullah, S. M.; Hall, J. E.; Bender, B. C.; McCurdy, D. R.; Tidwell, R. R.; Boykin, D. W. *J. Med. Chem.* **1999**, *42*, 3994; Tepe, J. J.; Madalengoitia, J. S.; Slunt, K. M.; Werbovetz, K. W.; Spoors, P. G.; Macdonald, T. L. *J. Med. Chem.* **1996**, *39*, 2188; Hyrup, B.; Egholm, M.; Nielsen, P. E.; Wittung, P.; Norden, B.; Buchardt, O. *J. Am. Chem. Soc.* **1994**, *116*, 7964.
15. Kovacs, Z.; Sherry, A. D. *Synthesis* **1997**, 759.
16. De Leon-Rodrigez, L. M.; Kovacs, Z.; Esqueda-Oliva, A. C.; Miranda-Olvera, A. D. *Tetrahedron Lett.* **2006**, *47*, 6937.
17. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1992.
18. *General procedure*: To a solution of 4-nitrophenyl active ester (1 mmol) in dichloromethane (20 mL) was added 1,4,7,10-tetraazacyclododecane (1 mmol). The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure. The residue was purified by column chromatography (chloroform/methanol/25% ammonia 5:1:0.1) to provide the desired product.
1-Ethoxycarbonyl-1,4,7,10-tetraazacyclododecane **5**: ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 1.25–1.29 (m, 3H), 2.70–2.72 (m, 5H), 2.84–2.86 (m, 9H), 3.51–3.52 (m, 5H), 4.15–4.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 46.7, 48.2, 49.2, 61.5, 157.7. HRMS (EI) calculated for $C_{11}H_{24}N_4O_2$: [M peak] m/z = 244.18993, found: 244.18908. Anal. Calcd for $C_{11}H_{24}N_4O_2$: C, 54.07; H, 9.90; N, 22.93. Found: C, 53.81; H, 9.86; N, 22.86.
1-*tert*-Butoxycarbonyl-1,4,7,10-tetraazacyclododecane **6**: ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 1.36 (s, 9H), 2.56–2.59 (m, 4H), 2.68–2.72 (m, 10H), 3.31–3.33 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 28.6, 46.8, 48.4, 49.0, 49.2, 79.8, 156.8. HRMS (EI) calculated for $C_{13}H_{29}N_4O_2$: [M+H peak] m/z = 273.2290, found: 273.2272. Anal. Calcd for $C_{13}H_{28}N_4O_2$: C, 57.32; H, 10.36; N, 20.57. Found: C, 57.03; H, 10.31; N, 20.46.
1-Benzyloxycarbonyl-1,4,7,10-tetraazacyclododecane **7**: ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ 2.73 (m, 2H), 2.82 (m, 2H), 2.97–3.01 (m, 6H), 3.12 (br, 2H), 3.66 (br, 2H), 3.72 (br, 2H), 5.18 (s, 2H), 7.34–7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 46.7, 48.4, 49.3, 49.4, 67.4, 128.2, 128.7, 137.0, 157.4. HRMS (EI) calculated for $C_{16}H_{27}N_4O_2$: [M+H peak] m/z = 307.2134, found: 307.2139. Anal. Calcd for $C_{16}H_{26}N_4O_2$: C, 62.72; H, 8.55; N, 18.28. Found: C, 63.03; H, 8.52; N, 18.18.