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Synthesis of azamacrocycles via a Mitsunobu reaction

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Abstract—Reaction of pernosylated diethylenetriamine and 2-substituted propane-1,3-diols in dry THF in the presence of triphenylphosphine and diisopropyl azodicarboxylate gives the corresponding protected 9-substituted 1,4,7-triazacyclodecanes. The Mitsunobu reaction was also used in the preparation of 3-substituted 1,5,9-triazacyclododecanes and macrocyclic pyridine derivatives.

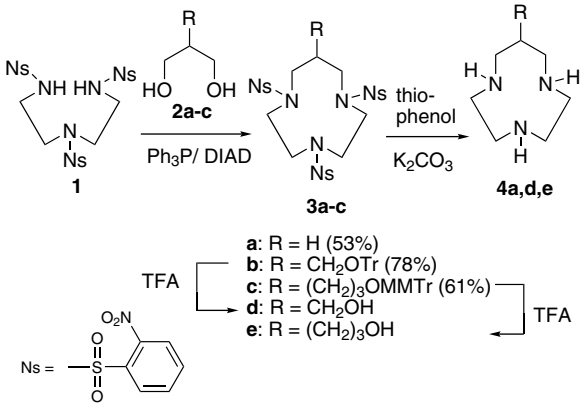
The metal chelates of azamacrocycles are widely used as radiopharmaceuticals[1] and MRI contrast agents.[2] They also have diagnostic applications.[3] Furthermore, europium(III) chelates based on 1,4,7-triazacyclododecane are among the brightest stable lanthanide(III) chelates synthesized.[4,5] Azacrown-functionalized oligonucleotides are potential artificial RNases.[6,7]

Most commonly, azamacrocycles are synthesized via the method of Richman and Atkins.[8] According to the latest modification of this reaction, the synthesis involves a reaction between a bifunctional electrophile (e.g., a dibromide or ditosylate) and a pernosylated amine in dry DMF at an elevated temperature in the presence of cesium or sodium carbonate.[9–11] Finally, the nosyl groups are removed with a thiol in the presence of base giving the desired azamacrocycle.

For several applications, such as for biomolecule conjugation, synthesis of carbon-substituted azacrowns with a reactive ω-substituent is needed. Although this type of molecule can be synthesized according to the method of Richman and Atkins,[12] alternative, simpler procedures are desirable. An elegant method for the preparation of azacrowns via orthoamides has been described,[13] but it is limited to the synthesis of 3-substituted 1,5,9-triazacyclododecanes.[6,7,14] Furthermore, the drastic conditions for orthoamide hydrolysis limit the nature of the tethering group.

Nosylamides are known to react with secondary and primary alcohols under standard Mitsunobu conditions giving the corresponding alkylated sulfonamides in excellent yield.[15,16] The reaction has also been successfully employed for the preparation of cyclic amines.[17] Thus, it was interesting to discover if the Mitsunobu reaction could be exploited for a one-pot preparation of azamacrocycles, simply by controlling the molecular ratio of the reactants. Accordingly, the amide **1**[8] was treated with an equimolar amount of various propane-1,3-diols (**2a–c**) in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in dry THF[18] (Scheme 1).

The reactions were complete in few hours at room temperature. After isolation by a silica gel column



Scheme 1.

Keywords: Mitsunobu reaction; Azacrown; Azamacrocycle.
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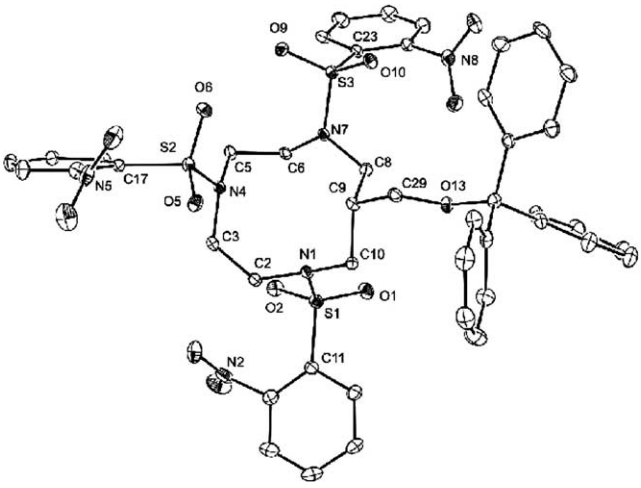


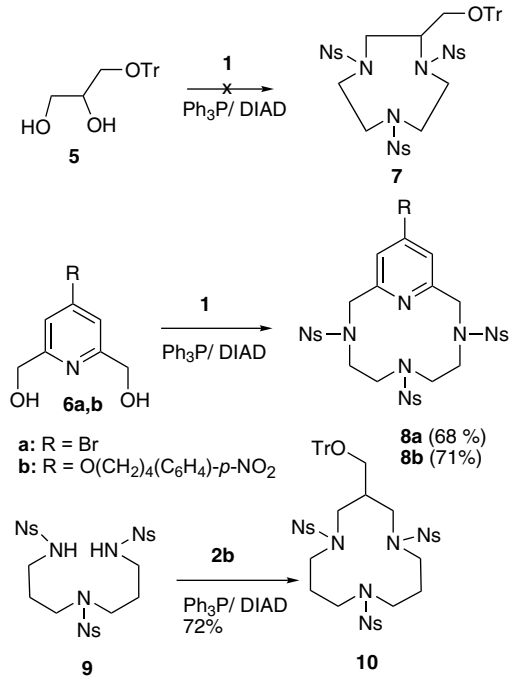
Figure 1. Thermal ellipsoid plot of **3b**. $3CHCl_3$ drawn at the 30% probability level. Chloroform molecules are omitted for clarity.

chromatography, the products were characterized as **3a**–**c**, based on their MS and ^1H NMR spectra. Furthermore, compound **3a** was chromatographically identical with material synthesized according to the latest modification of the method of Richman and Atkins, and compound **3b** gave crystals that enabled determination of the molecular structure by X-ray diffraction as **3b**. $3CHCl_3$ (Fig. 1).[19] It is worth noting that preparation of **3b**,**c** from **1** and the ditosylates of **2b**,**c** in DMF in the presence of Cs_2CO_3 were not successful. By contrast, in the Mitsunobu reaction, the highest yield (78%) was obtained using **2b**, a diol with a bulky trityl group in close proximity to the reaction centers. The azacrowns, **4**,[20] were isolated as their hydrochlorides after removing the protecting groups according to standard literature procedures.

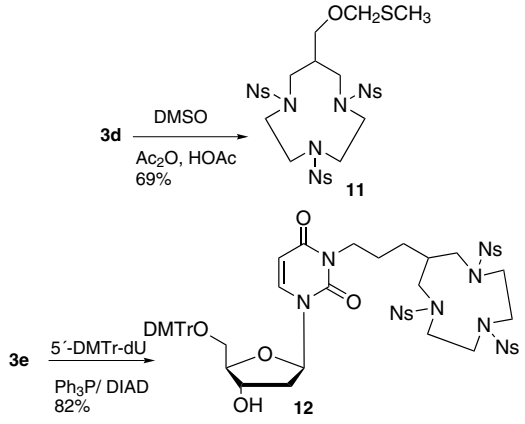
The applicability of the Mitsunobu reaction to the preparation of other types of macrocycle was tested by allowing **1** to react with 3-(trityloxy)-propane-1,2-diol **5** and 4-substituted pyridine-2,6-dimethanols, **6a**[21] and **6b**[22] (Scheme 2). While an attempt to synthesize **7** was unsuccessful, compounds **8a**,**b** were obtained in moderate yields.[23] Also, the reaction between pernosylated dipropylenetriamine, **9**,[8] and **2b** yielded the desired azamacrocycle, **10**.

When desired, the macrocycles synthesized can be easily converted to other derivatives. Two examples are shown in Scheme 3. Accordingly, treatment of **3d** with a mixture of DMSO, acetic acid, and acetic anhydride (5:1:2; v/v/v) overnight at an ambient temperature gave the corresponding methylthiomethyl ether, **11**, a versatile intermediate for further derivatizations.[24,25] Compound **3e**, in turn, was converted to a nucleoside derivative, **12**, via a Mitsunobu reaction with 2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-uridine.[26]

In summary, a simple method for the preparation of 9-substituted 1,4,7-triazacyclodecanes via a Mitsunobu reaction is described. As demonstrated, the cyclization reaction can also be used in the preparation of other



Scheme 2.



Scheme 3.

types of azacrown and macrocyclic pyridine derivatives. The diol counterpart must have two primary hydroxy groups in its structure. Bulky substituents in close proximity to the reaction centers seem to facilitate the reaction.

References and notes

1. Caravan, P.; Ellison, J. J.; McMurry, J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293–2352.
2. Anderson, C. J.; Welch, M. J. *Chem. Rev.* **1999**, *99*, 2219–2234.
3. Guo, Z.; Sadler, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1512–1531.
4. Takalo, H.; Hemmilä, I.; Sutela, T.; Latva, M. *Helv. Chim. Acta* **1996**, *79*, 789.
5. Ziessel, R.; Charbonniére, L. J. *J. Alloys Comp.* **2004**, *374*, 283–288.

6. Hovinen, J. *Bioconjugate Chem.* **1998**, *9*, 132–136.
7. Niittymäki, T.; Kaukinen, U.; Virta, P.; Mikkola, S.; Lönnberg, H. *Bioconjugate Chem.* **2004**, *15*, 174–184.
8. Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268–2270.
9. Burguete, M. I. U.; Escuder, B.; Caracía-Espana, E.; Luis, S. V.; Miravet, J. V. *Tetrahedron* **2002**, *58*, 2839–2846.
10. An, H.; Cook, P. D. *Tetrahedron Lett.* **1996**, *37*, 7233–7236.
11. Siaugue, J. M.; Segat-Dioury, F.; Sylvestre, I.; Favre-Réguillon, A.; Foos, J.; Madic, C.; Guy, A. *Tetrahedron* **2001**, *57*, 4713–4718.
12. Cox, J. P. L.; Craig, A. S.; Helps, I. M.; Jankowski, K. J.; Parker, D.; Eaton, M. A. W.; Millican, A. T.; Millar, K.; Beeley, N. R. A.; Boyce, B. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2567–2576.
13. Alder, R. W.; Mowlam, R. W.; Vachon, D. J.; Weisman, G. R. *Chem. Commun.* **1992**, 507–508.
14. Kim, R. D. H.; Wilson, M.; Haseltine, J. *Synth. Commun.* **1994**, *24*, 3014–3019.
15. Kurosawa, W.; Kan, T.; Fukuyama, T. *Org. Synth.* **2002**, *79*, 186.
16. For a recent review on Ns-amine chemistry, see: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.
17. Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267–6276.
18. Representative procedure: Compounds **1** (0.66 g, 1.0 mmol), **2c** (0.41 g, 1.0 mmol) and triphenylphosphine (0.79 g, 3.0 mmol) were dissolved in dry THF (25 mL). DIAD (0.59 mL, 3.0 mmol) was added in four portions during 15 min, and the reaction was allowed to proceed at room temperature for 4 h. All volatiles were removed in vacuo, and the residue was precipitated from diethyl ether. The precipitate was redissolved in dichloromethane, and the product **3c** was isolated from a silica gel column (eluent 0.5% MeOH in CH_2Cl_2; v/v) as a solid 120 °C. ^{1}H NMR ($CDCl_3$): δ 7.96–7.17 (15H); 6.82 (2H, d, $J = 8.9$); 4.06 (2H, m); 3.78 (3H, s); 3.61 (4H, m); 3.37 (2H, m); 3.25 (2H, m); 3.05 (4H, m); 2.57 (1H, m); 1.68 (2H, m). ESI-TOF MS: $[M+Na]^+$ obsd 1051.22 calcd for $C_{48}H_{48}N_6NaO_{14}S_3^+$ 1051.23.
19. Registration number CCDC 260264.
20. Compound **4d**·3 HCl ^{13}C NMR (D_2O): δ 61.20; 48.30; 44.45; 44.09; 34.74. ESI-TOF MS: $[M+H]^+$ obsd 174.1602; calcd for $C_8H_{20}N_3O^+$ 174.1601. Compound **4f**·3 HCl ^{13}C NMR (D_2O): δ 61.37; 50.66; 44.72; 44.08; 32.24; 28.38; 26.23. ESI-TOF MS: $[M+H]^+$ obsd 202.1916; calcd for $C_{10}H_{24}N_3O^+$ 202.1914. The hydrochlorides were converted to the corresponding free bases **4d**,**f** by passing through a column of Dowex-1 (OH^- form). For details, see Ref. 6.
21. Takalo, H.; Pasanen, P.; Kankare, J. *Acta Chem. Scand.* **1988**, *B42*, 373–377.
22. Compound **6b** was obtained by reduction of the corresponding 2,6-dimethyl ester (Hovinen, J. *Tetrahedron Lett.* **2004**, *45*, 5707–5709) with sodium borohydride in abs. ethanol.
23. The corresponding 4-unsubstituted derivative has been prepared using the method of Richman and Atkins, see Ref. 11.
24. Hovinen, J.; Azhayev, A.; Azhayeva, E.; Guzaev, A.; Lönnberg, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 211–217.
25. Hovinen, J.; Azhayev, A.; Guzaev, A.; Lönnberg, H. *Nucleosides Nucleotides* **1995**, *14*, 329–332.
26. Hovinen, J.; Hakala, H. *Org. Lett.* **2001**, *3*, 2471–2476.