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Short Communication

A Simple Synthesis of the Macrocycle 1,4,7,10-Tetraazacyclododecane

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Lanthanide complexes of 1,4,7,10-tetraazacyclododecane (cyclen) derivatives are widely used in magnetic resonance imaging.[1] The ligating ability is monitored by the nature of the *N*-substituents.[2] *N*-Substituted derivatives are generally prepared from cyclen by alkylation reactions.[3] Since the commonly used methods for the preparation of cyclen involve vigorous conditions, our aim has been to develop simple methodology for the preparation of cyclen under less harsh conditions thereby permitting the preparation of a range of *C*-substituted derivatives.[4] An alternative approach with dithiooxamide and triethylenetetraamine as substrates has recently been reported.[5] Before, in the most commonly used procedures for large scale syntheses, sulfonyl protected and activated di- or tri-ethylenetri- or tetra-amine has been reacted with appropriately activated α,ω-disubstituted ethylene derived reactants. For cleavage of the tosyl group in the cyclic product vigorous acidic reaction conditions are used.[6–9] Metal reduction in ammonia offers an alternative.[10] Oxo derivatives have been prepared by bridge forming reactions between two ethylenediamine molecules and appropriately activated acetic acid derivatives, and the lactam products reduced to amines by metal hydrides.[11]

The present method for the construction of cyclen is based on reports that triethylenetetramines react with glyoxal under phosphoric acid catalysis in aqueous solution to yield the tricyclic structure (**3**).[12] In this work glyoxal as template was reacted with triethylenetetraamine in ethanol. The major product from the reaction between one mole equivalent of 40% aqueous glyoxal solution, triethylenetetramine and triethylamine in ethanol solution was identified by NMR spectroscopy as the tricyclic product **2**. The alternative structure **3** has previously been obtained with acetonitrile as the solvent. The assembly of the reactants is probably reversible and therefore the relative product composition is solvent-dependent. The reaction was exothermic. In the ^{13}C NMR spectra three methylene carbons were seen at 45, 50 and 53 ppm and one methine carbon at 81 ppm. In the alternative structure **3** an additional methine signal would be expected because of non-equivalent methine carbons. In the ^{1}H NMR spectra there was only one signal for the methine proton consistent with structure **2**, whereas two signals and coupling would be expected for the methine protons in structure **3**. For the subsequent preparation of cyclen (**6**), however, either structure **2** or **3** will serve as an intermediate substrate because the same product **4** results from the bridge alkylation reaction. 1,2-Dibromoethane was used for the ring-forming dialkylation to furnish the desired product **4** in high yield. Structure **4** assigned to the product was confirmed by comparison with an authentic specimen, which was available from a reaction between cyclen and glyoxal in acetonitrile solution.[12] With ethanol as the solvent in this reaction, a close to quatitative yield of the tetracycle **4** resulted. FAB-MS supported the assigned molecular structure with *m/z* 195 (*M*−H). The signals at 52, 53 and 79 ppm in the ^{13}NMR spectra were also consistent with the structure assigned to the product.

Compound **4** was resistant to dilute acid degradation but was cleaved with partial fragmentation using strong acid and heating. The aminal function in the tetraamine **4**, however, was expected to exist in an intramolecular equilibrium involving an immonium functionality and an amine group indicated by structure **5**. A cleavage reaction was therefore designed to trap the immonium function eventually leading to the formation of a stable glyoxal derivative. This would allow cyclen to be liberated from its glyoxyl template. The concept was proved correct by warming **4** with excess hydroxylamine hydrochloride in

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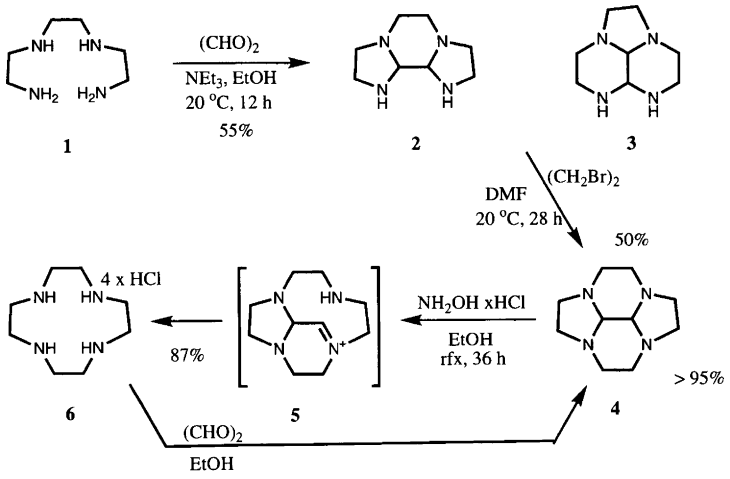

Scheme 1.

ethanol. The reaction proceeded well. The hydrolyzed product, as the tetrahydrochloride of cyclen, crystallized out from the cold solution in 87% yield whereas the oxime products of glyoxal remained in solution. The product has been identified as the HCl salt of cyclen by comparison with authentic material. The ^{1}H NMR spectra showed one singlet at 3.35 ppm and the ^{13}C NMR spetra showed one singlet at 46.7 ppm; the spectra are consistent with the symmetrical nature of cyclen.

In conclusion we have developed a simple three-step synthesis of cyclen from readily available starting materials and reagents.

Experimental

Perhydro-3,6,9,12-tetraazacyclopenteno[1,3-f,g]acenaphthylene[13] (**4**). An aqueous 40% solution of glyoxal (5 ml, 34.5 mmol) was added dropwise over 5 min with stirring to a solution of triethylenetetramine (5 ml, 34.5 mmol) and triethylamine (15 ml) in ethanol (50 ml). An exothermic reaction ensued. The mixture was stirred at ambient temperature overnight, the solvent evaporated off and the residual material subjected to flash chromatography on silica gel using MeCN–NH_3 (conc. aq.) 12:5 for elution; yield 3.50 g (55%) of a non-solid material in the main identified as *perhydropyrazo[1,2-a:2',1'-c]-diimidazole* (**2**). TLC [MeCN–NH_3 (conc. aq.) 12:5]: R_f 0.5. FAB-MS: 169 (M+H). ^{1}H NMR (300 MHz; D_2O): δ 2.56–2.48 (CH_2, t, 4 H), 2.9 (CH, s, 2 H), 3.2–3.0 (CH_2, m, 8 H). ^{13}C (75 MHz; D_2O): δ 45 (CH_2), 50 (CH_2), 53 (CH_2), 81 (CH). The product obtained was used in the subsequent reaction without further purification.

The product **2** (3.2 g, 19 mmol) was dissolved in DMF (30 ml), 1,2-dibromoethane (1.6 ml, 19 mmol) was added and the mixture stirred at ambient temperature. The progress of the reaction was monitored by TLC. An additional amount of 1,2-dibromoethane (0.4 ml) was added after 16 h, the stirring continued overnight when TLC showed full conversion of the substrate. The solvent was distilled off at reduced pressure and the residual material subjected to flash chromatography on silica gel using MeCN–NH_3 (conc. aq.)–EtOH (27:10:6) for elution; yield 1.50 g (50%) of a non-solid material. TLC [MeCN–NH_3 (conc. aq.)–EtOH 27:10:6]: R_f 0.2. FAB-MS: 195 (M+H). ^{1}H NMR (300 MHz; D_2O): δ 2.5–2.7 (CH_2, m, 8 H), 2.9–3.0 (CH_2, m, 8 H), 3.1 (CH, s, 2 H). ^{13}C (75 MHz; D_2O): δ 52.0 (CH_2), 53.0 (CH_2), 89.0 (CH, s).

1,4,7,10-Tetraazacyclododecane tetrahydrochloride (**6**). Hydroxylamine hydrochloride was added to a solution of perhydro-2a,4a,6a,8a-tetraazacyclopenteno[1,3-f,g]-acenaphthylene (0.2 g, 1.0 mmol) in ethanol (5 ml) and the mixture heated under reflux overnight. TLC showed about 40% conversion. An additional amount of hydroxylamine hydrochloride (0.35 g; 5 mmol) was added and the mixture heated under reflux for another 24 h. The product crystallized slowly from the cold reaction solution, and was collected and washed with ethanol; yield 0.28 g (87%). FAB-MS: 173 (M+H). ^{1}H NMR (300 MHz; D_2O): δ 3.35 (CH_2, s). ^{13}C (75 MHz; D_2O): δ 46.7 (CH_2).

References

1. (a) Izatt, R. M., Pawlak, K. and Bradshaw, J. S. *Chem. Rev. 95* (1995) 2529; (b) Lauffer, R. B. *Chem. Rev. 87* (1987) 901; (c) Broan, C. J., Cole, E., Jankowski, K. J., Parker, D., Pulukkody, K., Boyce, B. A., Beeley, N. R. A., Millar, K. and Millican, A. T. *Synthesis* (1992) 63; (d) Kang, S. I. and Tweedle, M. F. *Inorg. Chem. 32* (1993) 2912; (e) Broan, C. J., Jankowski, K. J., Kataky, R., Parker, D., Harrison, A. and Randall, A. M. *J. Chem. Soc., Chem. Commun.* (1990) 17392.
2. Bernhardt, P. V. and Lawrance, G. A. *Coord. Chem. Rev. 104* (1990) 297.
3. Li, Z. and Undheim, K. *Acta Chem. Scand. 52* (1998) 1247 and references therein.
4. Sandnes, R. W., Vasilevkis, J., Undheim, K. and Gacek, M. *PCT Int. Appl. WO 96 28,432* (1996); *Chem. Abstr. 125* (1996) P 301031c.

5. Weisman, G. R. and Reed, D. P. *J. Org. Chem. 61* (1996) 5186.
6. Richman, J. E. and Atkins, T. J. *J. Am. Chem. Soc. 96* (1974) 2268.
7. Lukyanenko, N. G., Basok, S. S. and Filonova, L. K. *J. Chem. Soc., Perkin Trans. 1* (1988) 3141.
8. Chavez, F. and Sherry, A. D. *J. Org. Chem. 54* (1989) 2990.
9. Stetter, H., Frank, W. and Mertens, R. *Tetrahedron 37* (1981) 767.
10. Panetta, V., Yaouanc, J. J. and Handel, H. *Tetrahedron Lett. 33* (1992) 5505.
11. Bradshaw, J. S., Krakowiak, K. E. and Izatt, B. M. *Chem. Heterocycl. Compd. 51* (1993) 539.
12. Jazwinski, J. and Kolinski, R. A. *Tetrahedron Lett. 22* (1981) 1711.
13. Weisman, G. R., Ho, S. C. H. and Johnson, V. *Tetrahedron Lett. 21* (1980) 335.

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