Pergamon

Tetrahedron Letters 41 (2000) 6527–6530

TETRAHEDRON LETTERS

Expeditious *N*-monoalkylation of 1,4,7,10-tetraazacyclododecane (cyclen) via formamido protection

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Received 19 June 2000; accepted 29 June 2000

Abstract

The reaction of cyclen **1** with chloral hydrate afforded *exclusively* 1,4,7-triformylcyclen **2** in high yield; the triprotected macrocycle was easily alkylated with various electrophiles in good to excellent yields. The alkaline removal of the formyl groups provided a selective entry into *N*-monosubstituted cyclen derivatives.

Since the discovery of the Gd(III) complex of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) as an efficient contrast agent (CA) for magnetic resonance imaging (MRI),[1] intensive research in this area has led to several related compounds entering late phase clinical trials and the marketplace.[2] Current CAs often have severe adverse effects (limited sensitivity due to poor tissue selectivity) so that more efficient and selective agents are being actively sought. One approach relies on the feasibility of tuning the lipophilicity of the ligands[2,3] by replacing a CH_2COOH moiety of DOTA with an appropriate alkyl group (e.g., HP-DO3A, DO3A-butrol)[2b] while maintaining high relaxation enhancement and modifying the biodistribution of metal complex-based drugs.

From a synthetic point of view, *N*-monoalkylated cyclen derivatives represent the key intermediates for the synthesis of DOTA-like ligands. Selective monoalkylation of cyclen can be run using two main strategies, i.e., direct alkylation of an excess of cyclen with the appropriate alkyl halide[4] or selective *N*-functionalization[5] followed by alkylation–deprotection steps. Although conceptually straightforward, the implementation of such strategies in an efficient and practical manner constitutes a demanding challenge in synthetic methodology.

By exploiting the finding that some acylating reagents (e.g. Cbz-Cl, Boc_2O)[6] afford under strictly controlled conditions mainly triprotected cyclen, we report here that triformylcyclen **2**,

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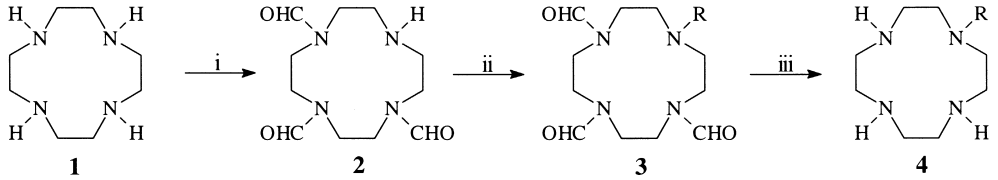
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01092-3

exclusively obtained from **1** in excellent yield, represents a key intermediate to *N*-monosubstituted cyclen derivatives (Scheme 1).



Scheme 1. (i) $CCl_3CH(OH)_2$, EtOH, 60°C; (ii) R–X, DMF, K_2CO_3, 80°C; (iii) 0.2 M NaOH, 80°C

Thus, compound **2** was prepared by reacting **1** (10 mmol) with commercially available chloral hydrate[7] (60 mmol) in ethanol (15 ml) at 60°C for 3 h. Fully or partially formylated derivatives were completely absent (by ESI-MS) from the reaction mixture even if the reaction was performed with a large excess of the reagent (up to 100 mmol). The usual workup followed by silica gel filtration (CH_2Cl_2:MeOH:NH_3, 9:1:0.1) afforded pure compound **2** in 92% yield. The reaction proceeded less satisfactorily in H_2O giving rise to **2** in 52% yield. Other formylating agents such as methyl or ethyl formate or formic acid[8] were tested but they proved less efficient in terms of chemical yields (20–35%) and longer reaction times (3 days at reflux with alkyl formates, 2 days at 100°C with formic acid). Owing to a hindered rotation of the N–CHO bonds, the NMR resonances appear as broad signals in the ^1H and ^{13}C NMR spectra and the structure of compound **2** was ascertained by HR-MS and elemental analysis. VT-NMR in DMSO-d_6 displayed coalescence of the C*H*O signals at 400 K. In justifying the experimental results, i.e. the exclusive formation of a triformyl derivative, we can only speculate that at least one basic nitrogen atom is required to assist intramolecularly the formylation reaction, possibly by general base catalysis. This hypothesis was supported by the isolation of tetraformylcyclen when either **1** or **2** was reacted with chloral hydrate in neat triethylamine.

The subsequent alkylation of **2** was performed with the appropriate electrophile in DMF at 80°C and in the presence of anhydrous K_2CO_3. It is remarkable that the monoalkylated products **3** were obtained in good to excellent yields even with long-chain alkyl halides (Table 1).

Table 1
Alkylation of triformylcyclen **2** with various electrophiles

Entry	R-X	Yield %
a	Bn-Br	90
b	Et-Br	80
c	n-Bu-Br	75
d	Allyl-Br	71
e	Propargyl-Br	68
f	n-$C_{10}H_{21}I$	78
g	n-$C_{16}H_{33}I$	72
h	9-Anthrylmethyl-Br	58
i	Ferrocenylmethyl-$N(CH_3)_3^+ I^-$	53

The interest in the synthesis of polymacrocyclic ligands[6b,9] prompted us to check the reactivity of **2** towards polyelectrophiles [e.g., 1,3-bis(bromomethyl)benzene, 1,4-bis(bromomethyl)benzene, 1,3,5-tris(bromomethyl)benzene] (Fig. 1).

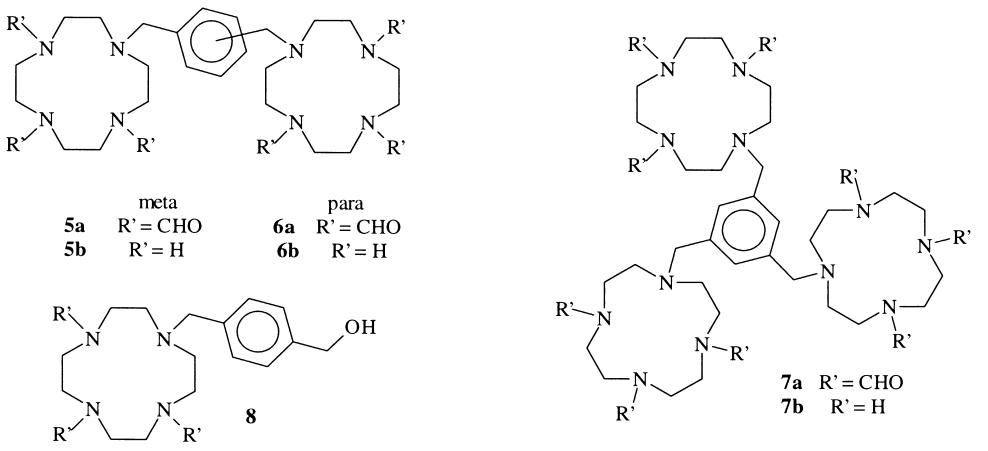


Figure 1.

We found that the best experimental conditions to perform the alkylation of **2** with these reagents required the use of anhydrous MeCN and K_2CO_3 as the base under reflux for 3 days. In this way, we could isolate compounds **5a**–**7a** in satisfactory isolated yields (73, 68 and 60%, respectively, after silica gel chromatography). By employing DMF as solvent in the alkylation step at 80°C, we could not avoid formation of the alcohol **8** arising from hydrolysis of the mono(bromomethyl) intermediate.

Once the alkylation products **3a**–**i**, **5a**–**7a** were isolated, conversion to the corresponding *N*-monoalkylated compounds **4a**–**i**, **5b**–**7b** was accomplished by treatment with 0.2 M NaOH at 80°C for 4 h with yields ranging from 85 to 95%. The free bases were characterized by ^{1}H NMR, ^{13}C NMR and MS spectra which were in full agreement with literature data.[5a,6b,9a]

The commercial availability of chloral at low cost combined with the operational simplicity and the complete selectivity makes this methodology extremely attractive for the synthesis of *N*-monoalkylated cyclen derivatives and polycyclen analogues. Furthermore, the protective step proceeded under neutral conditions and without exclusion of air and moisture, which is a significant improvement over current procedures.

Acknowledgements

This work was supported by CNR, Rome, through *Target project on 'Biotechnology'*. Professor S. Aime (University of Turin) is gratefully acknowledged for his interest and helpful discussions.

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