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An efficient one-pot route to symmetrically and unsymmetrically substituted 1,4,7-triazacyclononanes also results in the isolation of a stable macrocyclic aminal

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Abstract

A one-pot methodology has been developed for the direct synthesis of symmetrically and unsymmetrically *N*-substituted derivatives of 1,4,7-triazacyclononane. In the course of these studies the unexpected eight-membered cyclic aminal **7** has been isolated via an acid-catalysed rearrangement of enamine **5**.

Keywords: aminals; aza compounds; enamines; macrocycles; polyamides; polyazacycloalkanes.

The preparation of nitrogen macrocycles in which the tertiary nitrogen atoms are unsymmetrically substituted is currently an area of considerable interest due to the diverse range of chemical properties[1] and biomedical applications[2] that their metal complexes exhibit. Considerable success has been achieved in the selective alkylation of tetra-aza macrocycles, particularly cyclen;[3] however, current strategies towards unsymmetrically *N*-substituted derivatives of the related facially coordinating 1,4,7-triazacyclononane are more limited. These generally either involve statistical alkylation of the free macrocycle,[4] dialkylation of the mono-tosylamide[1b,5] or the derivatisation of the macrocyclic orthoamide.[6] All of these procedures have been widely adopted but, in addition to the synthetic drawback of firstly synthesising the macrocycle,[7] the former alkylation methodology necessitates the separation of the required product from the statistical reaction mixture, while the latter involves further protection/deprotection chemistry en route to the macrocycle with the desired substitution pattern. We were interested in investigating the viability of a general cyclisation protocol which could furnish symmetrically and unsymmetrically substituted derivatives of 1,4,7-triazacyclononane directly as depicted in Scheme 1. Although similar reactions have been previously reported for the preparation of **2** and other macrocyclic polyamines, these methodologies are more limited as they only lead to symmetrically substituted macrocycles.[8]

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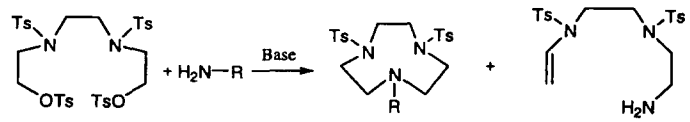


1

2 R = Ts
3 R = Bn
4 R = H

5

Scheme 1. One-pot synthetic route to symmetrically and unsymmetrically substituted 1,4,7-triazacyclononanes

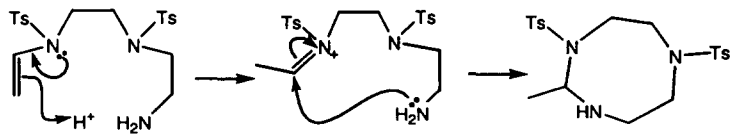
Table 1
Summary of optimised one-pot cyclisation reactions

Entry	R	Base	Solvent	Reaction time/d	Temperature /°C	Product	Yield (%)
1	Ts	K_2CO_3	DMF	5	100	**2**	52[a]
2	Ts	K_2CO_3	CH_3CN	10	reflux	**2**	100
3	Bn	Cs_2CO_3	DMF	5	100	**4**	30[b]
4	Bn	K_2CO_3	CH_3CN	6	reflux	**3**	70
5	Z	K_2CO_3	DMF	2	reflux	**4**	70[c]
6	allyl	K_2CO_3	DMF	6	100	**4**	25[d]

[a]Isolated by flash chromatography on silica gel (ethyl acetate:40:60 petroleum spirits).
[b]**4** is isolated from multiple side products,including enamine **5**,after column chromatography on silica gel (ethyl acetate:40:60 petroleum spirits).
[c]**4** isolated by column chromatography on silica gel (ethyl acetate:40:60 petroleum spirits) followed by recrystallisation from ethanol.
[d]**4** isolated by column chromatography on silica gel (ethyl acetate:40:60 petroleum spirits).
Z = $PhCH_2OC(O)$-

In general, these cyclisation reactions proceed efficiently in good to excellent yields[9] (Table 1) and the pure macrocycles can be isolated simply by filtration, to remove insoluble materials, followed by evaporation and recrystallisation. It is interesting to note that in the case of entries 3, 5 and 6 only the deprotected macrocycle **4** can be isolated. There is literature precedent for such deprotections under basic conditions for entries 5 and 6.[10] At this stage we have no explanation for the loss of the benzylic group in entry 3.

In addition to the desired macrocyclic products, on several occasions we also observed signs of an identifiable side product, apparently resulting from an E2-elimination, which was particularly prevalent for entry 3. Our attempts to separate this material from the target macrocycle by column chromatography on silica gel did not result in any elimination product being isolated and we were surprised to find that the eight-membered macrocyclic aminal **7** together with **4** were the only materials we could isolate. We hypothesised that the macrocyclic aminal had formed as a result of an *endo* cyclisation of iminium ion **6**. We were able to demonstrate this after **5** was isolated by column chromatography on neutral alumina and subsequently converted to aminal **7** by the addition of either silica gel or HBF_4; in addition the reaction also proceeds smoothly under Lewis acid catalysis using $BF_3 \cdot Et_2O$ (Scheme 2). The NMR data for **7** are entirely consistent with those reported in the literature for related aminals,[11] particular similarity being observed in the data for **7** and 1,3-diacetyl-2-methylhexahydropyrimidine.[11b] Aminal **7** proves to be remarkably stable, showing no signs of decomposition after prolonged storage and can even be readily protonated without any signs of decomposition by HBF_4 and absolute ethanol; in the presence of *p*-toluenesulfonic acid monohydrate, however, rapid decomposition occurs.



5 6 7

Scheme 2. Proposed mechanism for the formation of aminal **7** from enamine **5**

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9. All cyclisation reactions were performed in an identical manner which is typified by the synthesis of **3**. A solution of **1** (1.0 g, 1.30 mmol), benzylamine (157 μl, 1.43 mmol) and potassium carbonate (396 mg, 2.87 mmol) in dry acetonitrile (15 ml) was stirred at reflux under nitrogen for 6 days. After cooling to room temperature, the insoluble material was removed by filtration and the filtrate concentrated in vacuo. The crude material was purified by crystallisation from hot ethanol to give **3** (480 mg, 70%) as white crystals. All new compounds were homogeneous by TLC, with ^{1}H, ^{13}C and IR spectra consistent with their formulations, in addition their mass spectra gave the expected molecular ions.
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