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# Annulated carbamates are precursors for the ring contraction of the adamantane framework†

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We report a protocol for the one-pot two-step synthesis of noradamantane methylene amines. The first step is the triflic acid-promoted decarboxylation of adamantane carbamates, which causes rearrangement of the adamantane framework to form noradamantane iminium salts, which are reduced to amines in the second separate step.

## Introduction

Noradamantane (adamantane lacking one methylene unit) derivatives such as amines,<sup>1</sup> acids,<sup>2</sup> methylene alcohols,<sup>3</sup> and others<sup>4</sup> are useful building blocks in organic synthesis. Together with adamantane derivatives,<sup>5</sup> they are typically used to make target molecules more lipophilic, bulky or conformationally rigid, which is exploited in drug<sup>6</sup> and catalyst design<sup>7</sup> or in materials science for preparation of polymers, dendrimers, and light emitting and other special devices.<sup>8</sup> Noradamantane compounds can also serve as precursors for the synthesis of adamantane derivatives *via* ring expansion methods.<sup>9</sup> Various simple noradamantane derivatives (*e.g.* containing methylene amine group) exhibit biological activity and were tested as inhibitors (Fig. 1).<sup>10</sup>

Compared to adamantane ( $T_d$  point group), the noradamantane skeleton ( $C_{2v}$ ) has a lower symmetry and exhibits different reactivity towards oxidation reactions, which complicates the synthesis of on cage-substituted derivatives.<sup>11</sup> Noradamantane framework can be prepared by skeletal rearrangement of deltacyclane,<sup>11</sup> from 4-protoadamantanone<sup>12</sup> or from suitable adamantane precursors such as 1,3-adamantane diols.<sup>13</sup> Most syntheses of noradamantane cage compounds start from adamantane-2-one.<sup>14</sup> This substantially limits the preparation of (on cage)-substituted derivatives as there are not many  $C_2$  symmetric substrates available or easily synthesizable (Fig. 2).

We have recently contributed with a new method for the preparation of noradamantane carbaldehydes based on the decarboxylation of annulated *N*-methylated adamantane carbamates followed by a nucleophilic 1,2-alkyl shift and hydrolysis of the resulting iminium salts.<sup>15</sup>

## Results and discussion

In this work, we focus on the triflic acid promoted decarboxylation of *N*-unsubstituted carbamates, which leads to the ring contraction of the adamantane framework by nucleophilic 1,2-alkyl shift<sup>16</sup> producing noradamantane carbaldiminium salts, and the one-pot reduction of the resulting iminium salts to noradamantane methylene amines was performed in the same pot subsequently using  $\text{LiAlH}_4$  (Fig. 2). The decarboxylation of the carbamate with triflic acid in the presence of HX was performed to get a halogen in the position next to an amino group on the adamantane framework to have possibility to study all steps of the cascade process (decarboxylation and 1,2-alkyl shift) separately. The ring contraction of the adamantane framework containing a leaving group in the position next to an amine is now described in acidic and basic media and is analogical to aziridine formation<sup>17</sup> for non-bridged flexible aliphatic systems (Fig. 3).

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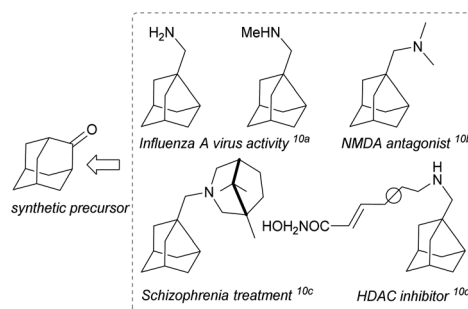


Fig. 1 Bioactive noradamantane-3-methylene amine derivatives.



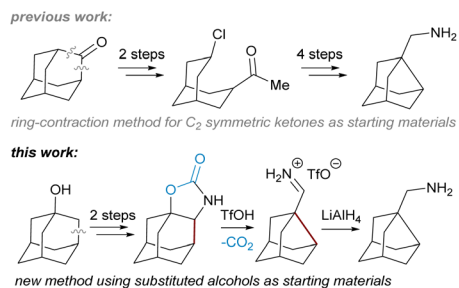


Fig. 2 New approach to noradamantane-3-methylene amines from adamantan-1-ol.

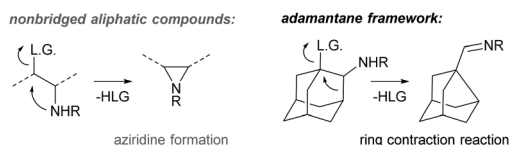
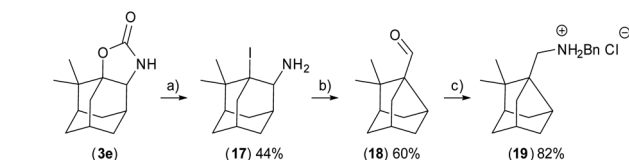


Fig. 3 Nucleophilic rearrangement reaction of the adamantane framework containing a leaving group next to the amino group.

The cyclic carbamate **3a** was prepared in two steps from adamantan-1-ol **1a** and was used as a model compound for optimisation of the reaction conditions.<sup>18</sup> The optimal conditions; 2 equivalents of trifluoromethanesulfonic acid, 1,2,4-trichlorobenzene as a solvent, 0.06 M dilution, 120 °C and 4 h reaction time for the decarboxylation and rearrangement step.

The reduction of the *in situ* formed iminium salt (**Int1-OTf**, Fig. 5A) was performed by adding LiAlH<sub>4</sub> and THF to the reaction mixture and stirring at 25 °C for three hours. This method was used for the rearrangement and reduction of four various starting materials substituted on the adamantane cage leading to compounds **5**, **9**, **11**, **13** (Fig. 4). For the decarboxylation and reduction of *N*-substituted carbamates (Me and 2,2'-dichlorobenzyl) the reaction conditions (dilution 0.5 M, temperature 140 °C and reaction time 16 h) were changed.



Scheme 1 Rearrangement reaction of **17** at basic media to imine intermediate, which is *in situ* hydrolysed to aldehyde **18** and amination reaction of **18** to amine hydrochloride salt **19**. (a) TfOH/KBr/CH<sub>2</sub>Cl<sub>2</sub>, 40 °C; (b) K<sub>2</sub>CO<sub>3</sub>/H<sub>2</sub>O, 100 °C; (c) (1). PhCH<sub>2</sub>NH<sub>2</sub>/MgSO<sub>4</sub>/THF, 25 °C; (2). LiAlH<sub>4</sub>/THF/25 °C; (3) HCl/Et<sub>2</sub>O.

Compound **7** was crystallised and characterised by X-ray crystallography (Fig. 4). Starting materials **3e**, **4ea** (*N*-Me carbamate), and **4eb** (*N*-CH<sub>2</sub>Ar carbamate) undergo the reaction sequence, but the final products are not obtained in required purity and the final amine **19** was prepared by reductive amination from the aldehyde **18** (Scheme 1). The amines can be stored as hydrochloride salts or protected with *e.g.* Boc group (compounds **6** and **10**). Diastereomers of **9** were resolved by fractional crystallisation of the Boc-protected compound **10** in pentane.<sup>19</sup> Isomer **10-I1** was recrystallised and its configuration was determined using X-ray crystallography (Fig. 4).

The proposed mechanism of the ring contraction reaction cascade is the triflic acid promoted decarboxylation of **3** to form intermediate **Inta-OTf**, followed by a nucleophilic 1,2-alkyl shift to form the iminium salt **Int1-OTf**. The calculated (DFT method) difference in stability of the intermediate cations **Inta**<sup>+</sup> and **Int1**<sup>+</sup> is  $\Delta G = 16.5 \text{ kcal mol}^{-1}$  (Fig. 5E).

The iminium salt intermediate **Int1-OTf** is reduced in the next step using LiAlH<sub>4</sub> to form the product **5** (Fig. 4) or it can be trapped by other nucleophiles such as a nitrile using the Strecker reaction with TMSCN to form compound **15**, precursor for non-biogenic  $\alpha$ -amino acids<sup>20</sup> as demonstrated on the synthesis of compound **16** (Scheme 2).

The ring-contraction reaction was then studied using compounds containing halogens as a leaving group next to an

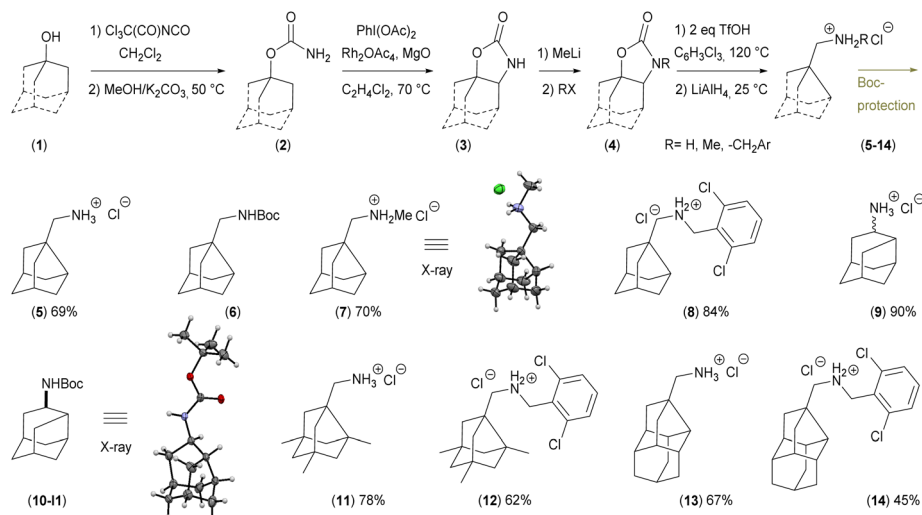
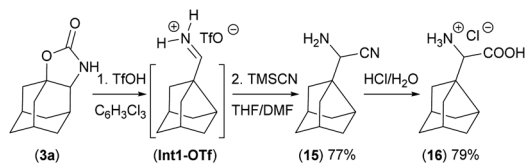


Fig. 4 Scope of the new transformation. Yields of isolated products are stated.





**Scheme 2** Trapping of the iminium intermediate (**Int1-OTf**) by TMSCN and preparation of the  $\alpha$ -amino acid hydrochloride salt **16**.

amine group mimicking the reactive intermediate **IntA-OTf**, which is obtained after the decarboxylation step (Fig. 5A).

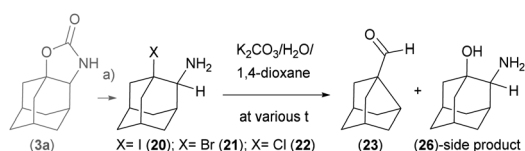
First, we performed the ring contraction of **24** using MeLi to deprotonate an amine group, to generate imine **25**, which was isolated and characterised (Fig. 5C).

Then we prepared compounds **20**, **21**, **22** (ref. 18) and studied the ring contraction reaction in a polar solvent in analogy to  $S_N1$ -substitution reactions. Thermal cleavage of 1-iodo derivative **20** in a polar solvent mixture (1,4-dioxane/ $K_2CO_3$  water solution), provided the ring contracted imine **Int1-I**, which was *in situ* hydrolysed to aldehyde **23** (Fig. 5D).

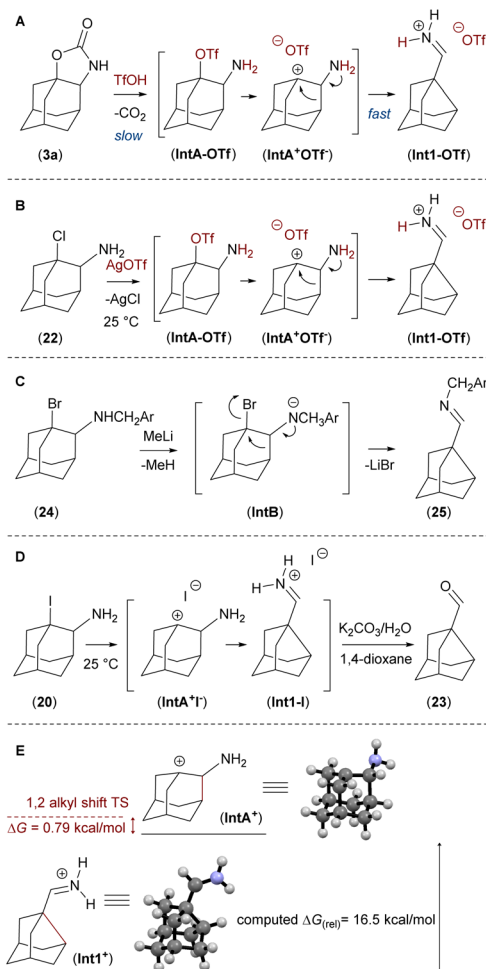
Kinetics of the thermal rearrangements were studied with compounds **20**, **21** and **22** in 1,4-dioxane/ $K_2CO_3$  water solution mixture using  $^1H$ -NMR measurements at various temperatures and concentrations (Scheme 3).

These reactions resemble  $S_N1$ -substitution reactions following the same trend: iodo-derivative **20** undergoes the ring contraction reaction already at room temperature, slower ring contraction reaction proceeds with bromo-derivative **21** and the slowest reaction occurs with chloro-derivative **22**. The product of a substitution side reaction, 2-amino adamantane-1-ol **26** was detected, isolated and characterised (Scheme 3). Apparent first order kinetic constants estimated for solvolysis of 1-halogeno-2-amine adamantanes to the main product at 50 °C are within the range:  $k = (130 \pm 20) \times 10^{-5} s^{-1}$  for X = I;  $k = (125 \pm 20) \times 10^{-5} s^{-1}$  for X = Br; and  $k = (3 \pm 0.2) \times 10^{-5} s^{-1}$  for X = Cl. For determination of kinetic constants of solvolysis of individual 1-halogeno-2-amine adamantanes see ESI.†

Taking all data into account, the rate limiting step of the ring contraction reaction is the decarboxylation of compound **3** to the intermediate **IntA-OTf**. The computed barrier of the next step 1,2-alkyl shift between **IntA**<sup>+</sup> and **Int1**<sup>+</sup> is only 0.79 kcal mol<sup>-1</sup> (Fig. 5E).<sup>21</sup> This is in line with an experiment where intermediate **IntA-OTf** was generated from compound **22** by adding AgOTf to the solution at room temperature and instantaneous formation of the imine **Int1-OTf** was observed (Fig. 5B).<sup>9</sup>



**Scheme 3** Kinetics of the thermal rearrangement reactions in a polar solvent mixture. (a) TfOH/KX/ $CH_2Cl_2$ , 40 °C and neutralisation; (b)  $K_2CO_3/H_2O/1,4$ -dioxane, VT-exp.



**Fig. 5** (A): Ring-contraction reaction of the adamantane framework in acidic medium; (B): generation of the reactive intermediate **IntA-OTf** from chloro-derivative **22**; (C): ring-contraction reaction of **24** with strong base; (D): ring-contraction reaction of **20** in polar basic medium; (E): computed relative stability of intermediate **IntA**<sup>+</sup> versus target structure **Int1**<sup>+</sup> using DFT method B3LYP/def2-TZVPP and computed  $\Delta G$  for transition state of the 1,2-alkyl shift.

## Conclusions

We have shown that adamantane based cyclic carbamates are suitable precursors for ring contraction of the adamantane framework and that the formed iminium moiety can be reduced or trapped by a nucleophile gaining access to noradamantane amino derivatives. The ring contraction reaction can be performed under acidic or basic conditions from suitable starting materials, and proceeds through imine intermediates. The ring contraction reaction of adamantane based 2-amino-1-alcohols as starting materials is part of our future studies.

## Author contributions

R. H. and O. H. performed the synthetic work. I. C. is responsible for X-ray crystallographic analysis, F. K. for NMR measurements and O. M. for kinetic studies.



## Conflicts of interest

There are no conflicts to declare.

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