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

Compared to adamantane (Td point group), the noradamantane skeleton (Cnv) has a lower symmetry and exhibits different reactivity towards oxidation reactions, which complicates the synthesis of on cage-substituted derivatives. Noradamantane framework can be prepared by skeletal rearrangement of deltacyciane, from 4-protoadamantanone or from suitable adamantane precursors such as 1,3-adamantane diols. Most syntheses of noradamantane cage compounds start from adamantant-2-one. This substantially limits the preparation of (on cage)-substituted derivatives as there are not many C2 symmetric substrates available or easily synthetizable (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.

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 producing noradamantane carbaldehyde salts, and the one-pot reduction of the resulting iminium salts to noradamantane methylene amines was performed in the same pot subsequently using LiAlH4 (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 analogous to aziridine formation for non-bridged flexible aliphatic systems (Fig. 3).

Fig. 1 Bioactive noradamantane-3-methylene amine derivatives.
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. 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 LiAlH4 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.

Compound 7 was crystallised and characterised by X-ray crystallography (Fig. 4). Starting materials 3e, 4ea (N-Me carbamate), and 4eb (N-CH2Ar 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. 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+ and Int1+ is \( \Delta G = 16.5 \text{ kcal mol}^{-1} \) (Fig. 5E).

The iminium salt intermediate Int1-OTf is reduced in the next step using LiAlH4 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 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...
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 SN1-substitution reactions. Thermal cleavage of 1-iodo derivative 20 in a polar solvent mixture (1,4-dioxane/K2CO3 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/K2CO3 water solution mixture using 1H-NMR measurements at various temperatures and concentrations (Scheme 3).

These reactions resemble SN1-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-halogen-2-amine adamantanes see ESL.†

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* and Int1* is only 0.79 kcal mol$^{-1}$ (Fig. 5E). 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).9

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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