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# 4-Aziadamantan-1-amine: synthesis, reactions and cyclodextrin complexes†

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**Abstract**—A new and potentially therapeutic diazirine, 4-aziadamantan-1-amine, was synthesized. Structural characterization also included single crystal X-ray diffraction analysis. Photolysis of the title compound in the solid phase afforded an azine. In contrast, pyrolysis in the gas phase gave two intramolecular carbene insertion products in a 4:1 ratio. A rationale for the observed diastereoselectivity is offered based upon ab initio calculations. Finally, inclusion compounds of the title compound with α- and β-cyclodextrin were prepared. A 2:1 complex bearing two hosts was formed with α-cyclodextrin and a 1:1 complex was obtained with β-cyclodextrin. The association constants were determined via induced circular dichroism (ICD) analysis. 

## 1. Introduction

Diastereoselective additions of nucleophilic reagents to adamantan-2-one (**1**) substrates are currently under active investigation (e.g. hydride reduction of the carbonyl group).[1,2] Much effort has been made to explain the influence of remotely substituted pendant groups. γ-Substituted adamantanones are rigid structures that are considered to be *sterically* unbiased with regard to reactions at the carbonyl group. Yet an electronegative substituent, such as a methoxy or an iodo group, at the γ-position proved to be especially influential because it led to 65% *anti* reduction.[3] To explain this facial selectivity,[4] hyperconjugation,[5] electrostatic interactions,[6] and distortion of the geometry of the precursor causing a steric preference for the reagent's attack[7] have been suggested. All of these explanations have been the subject of intense discussions. However, since it seems to violate frontier orbital theory, the Cieplak model[5c,d] gave rise to serious criticism.[2b,8] So what effect is truly responsible for causing this diastereoselectivity? This question is still a matter of passionate debate.[9]

We are investigating the influence of substituents at the γ-position on the intra- and intermolecular diastereoselectivities of carbenes generated from the corresponding 2-aziadamantanes.[10] This, as well as studies with cyclodextrin complexes of 4-aziadamantan-1-ol (**10**),[11] stimulated the need for the preparation of the hitherto unknown 4-aziadamantan-1-amine (**8**). Coincidentally, diazirine **8** might have therapeutic applications. Adamantan-1-amine and its *N*-substituted derivatives, have shown promise as remedies against the influenza virus, and also as *anti*-HIV and *anti*-Parkinson's agents.[12] Moreover, biochemists have found use for diazirines as photo-affinity labels.[13]

## 2. Results and discussion

A new strategy was devised for the synthesis of 5-aminoadamantan-2-one (**6**) (Scheme 1).[14] The key step consists of the amidation of **4** to give **5**. The HBr released during this transformation led to a partial loss of the ketal moiety of **5**. Nevertheless, the entire crude mixture was subjected to the subsequent deprotection step. The yield of the conversion of **4** to **6** was found to be 92%.

The conventional method according to Adcock[3b] includes a Koch–Haaf carboxylation and a subsequent Hofmann rearrangement and degradation. It is the logical consequence of classical adamantane chemistry.[15] The new method applied here, however, is more

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† Carbene Rearrangements. Part 56. For Part 55, see: Rosenberg, M. G.; Brinker, U. H. *J. Org. Chem.* **2001**, *66*, 1517.

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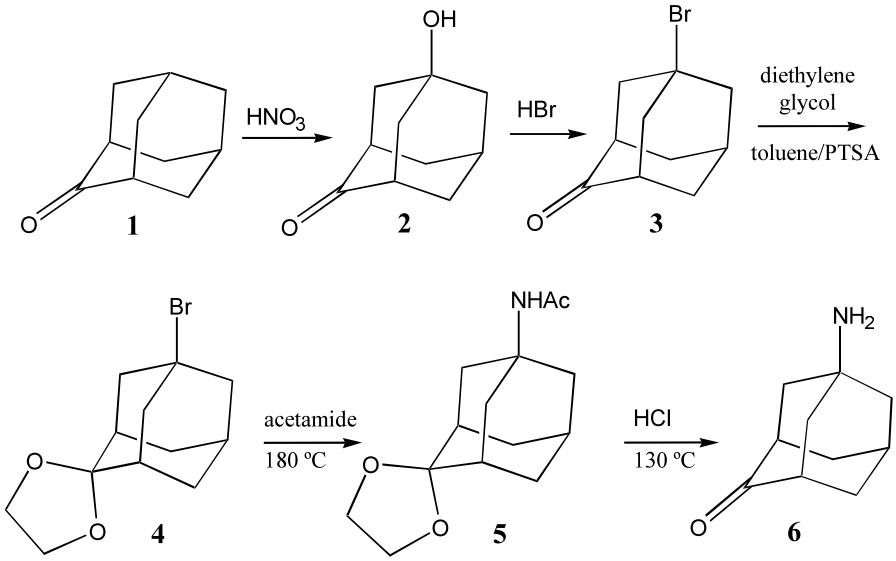



**Scheme 1.** Synthesis of 5-aminoadamantan-2-one (**6**) from adamantan-2-one (**1**).

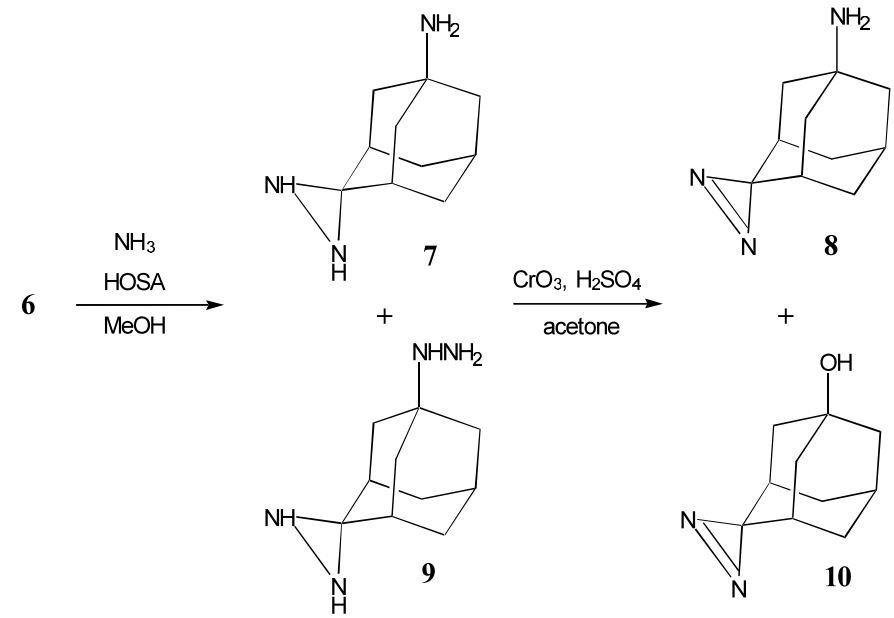
straightforward and also affords **6** (from **2**) in a higher overall yield (50% instead of 41%).

The synthesis of diazirine **8** followed established procedures (Scheme 2).[16] The reaction of **6** with hydroxylamine-*O*-sulfonic acid (HOSA)[17] was performed at −15°C in methanolic ammonia. The putative diaziridines **7** and **9** were not isolated[18] but directly oxidized after drying. In addition to starting material **6**, 4-aziadamantan-1-amine (**8**) and 4-aziadamantan-1-ol (**10**) were obtained in 26 and 8% yield, respectively. The separation of **8** was accomplished by column chromatography.[19]

The formation of **8** represents the first diazirine synthesis in the presence of a free amino group. Diazirine syntheses whereby the amino group was introduced at a later stage, as well as with *N*,*N*-alkylamine substituted ketones are already known.[20] As shown in Scheme 2, the amino group in **6** can also react with HOSA to afford 4-aziadamantan-1-ol (**10**).[17] The title compound **8**[21] was crystallized from isopropanol as its hydrochloride (Fig. 1, Table 1).[22]

Currently, very few diazirines have been investigated by means of X-ray structure analysis.[23] The bond lengths and angles observed for the diazirine moiety of **8** agree with those of **10**.[11b]

Diazirine **8** was photolyzed in the solid state and pyrolyzed in the gas phase (Scheme 3).[16b,24] The solid state photolysis produced the anticipated azine bis(5-aminoadamantan-2-ylidene)hydrazine (**13**, purity: ca. 90%). In contrast, the gas phase pyrolysis afforded the




**Scheme 2.** Formation of diazirines **8** and **10** from aminoketone **6**.

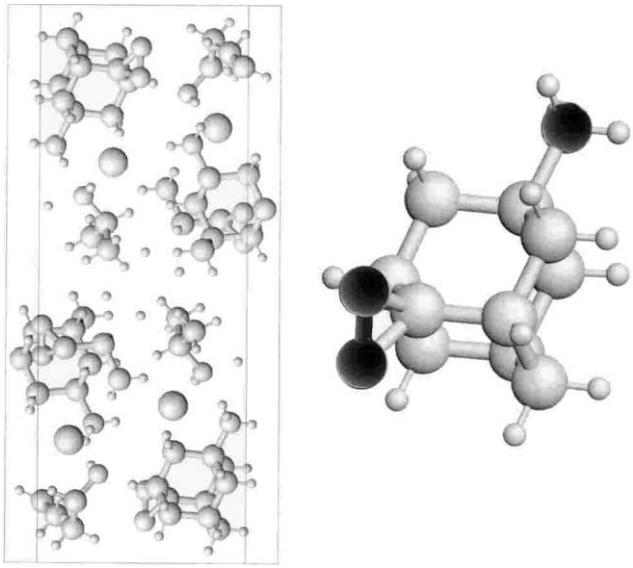


**Figure 1.** Unit cell of **8** according to X-ray structure analysis.

**Table 1.** Selected bond lengths and angles for 4-Azi-adamantan-1-amine (**8**)

| | |
|---|---|
| N–C–N angle (°) | 49.627 |
| C–N length (Å) | 1.48 |
| N=N length (Å) | 1.24 |

two possible 1,3 C–H insertion products, 4,6-didehydroadamantan-1-amine (**11**) and *rac*-2,4-didehydroadamantan-1-amine (**12**), in a 4:1 ratio.

Ab initio calculations[25] of 5-hydroxyadamantan-2-ylidene[10] show that the unoccupied *p*-orbital of the carbene (LUMO) participates in both the C1–C8 and the C3–C10 bonds. Moreover, the occupied $sp^2$-orbital (HOMO) is bent away from the substituent and, consequently, the carbene carbon is inclined toward the *anti*-side by $\theta$ = ca. 7.4°.

A similar result was observed for the ground state of 5-aminoadamantan-2-ylidene (Fig. 2). The bridge with the divalent carbon is bent away from the amino group by 6.8°.

These factors are responsible for the intramolecular 1,3 C–H insertion of the divalent carbon of **14** during the pyrolysis of **8** to preferentially afford the symmetrical *anti*-product **11**. The more electronegative the substituent is, the more pronounced is this preference.[2a] Indeed, when **14** is compared with 5-hydroxyadamant-2-ylidene, the carbene bridge of **14** is bent a little less—but in the same direction. This somewhat lesser bending in **14** could be responsible for the less pronounced ratio of 4:1 obtained from **14** versus 9:1 from 5-hydroxyadamant-2-ylidene.[10] But this conclusion must be considered premature without further studies employing more substituents of different electronegativities at C5.

Title compound **8** formed cyclodextrin (CyD) inclusion complexes with both α- and β-cyclodextrin.[26] The $^1$H NMR analyses of the complexes proved that a 2:1 complex (i.e. **8**@(α-CyD)$_2$) was ormed with α-cyclodextrin but that a 1:1 complex (i.e. **8**@β-CyD) was obtained with β-cyclodextrin. ROESY spectra gave insight regarding the structural aspects of the inclusion compounds. And ICD spectra allowed for the determination of association constants.

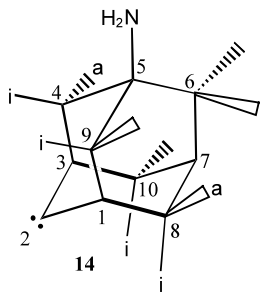
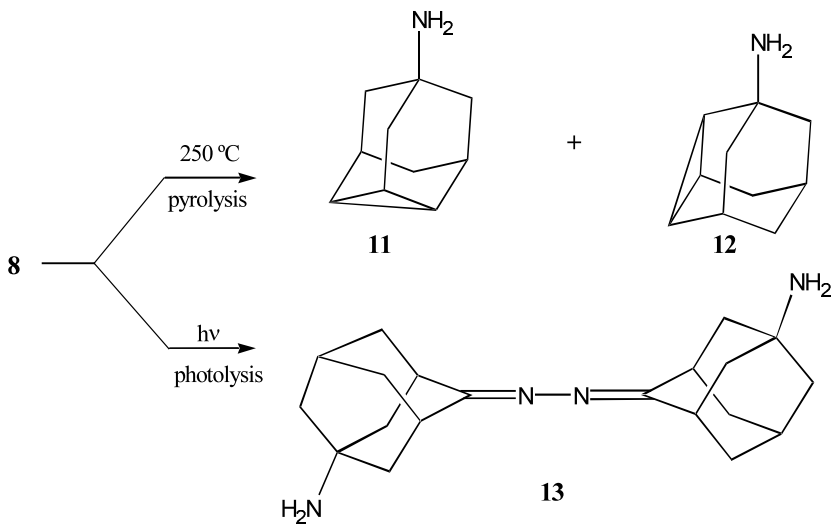



**Figure 2.** 5-Aminoadamant-2-ylidene (**14**).




**Scheme 3.** Reactions of diazirine **8**.

According to ROESY,[27] the diazirine moiety in both complexes is embedded within the CyD cavity (Fig. 3). Inside α-CyD, a NOE occurs between H3, H5, $H_i2$, $H_i6$, $H_i9$, and $H_i10$ of diazirine **8** and only H3 of the CyD host. But from the spectra of **8**@β-CyD, cross-peaks to H5 indicate that the diazirine group is even deeper within the host cavity. And the amino group is situated above the larger rim.

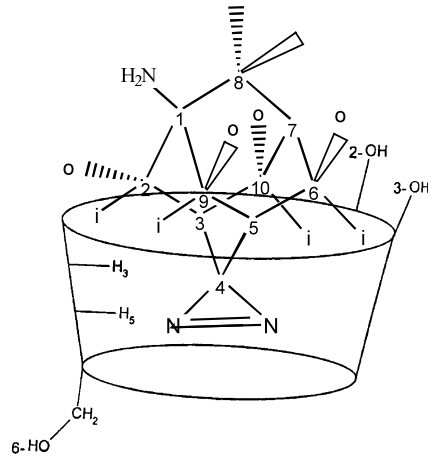



**Figure 3.** Diazirine **8** entrapped within a cyclodextrin (CyD). The guest is more deeply lodged within β-CyD than in α-CyD. But in the α-CyD inclusion compound of **8**, a second host serves to fully encapsulate the guest.

The achiral diazirine chromophore gives rise to an ICD in both chiral host–guest complexes.[28] Although the sign of the ICD Cotton effect was positive and weak for the **8**@β-CyD complex, it was negative and strong for **8**@$(\alpha\text{-CyD})_2$. However, drawing conclusions regarding the local orientation of a guest within the two CyD complexes solely based upon the sign of the ICD signal is problematic.[28b]

The obtained data were analyzed using a Scatchard plot.[28a,29] Hence, the association constants of both complexes of **8** with α- and β-CyD were determined. In pure water, the association constants are significantly larger than in the 30% aqueous EtOH.[28a] This has to be considered when comparing the values in Table 2.[30]

**Table 2.** Association constants for CyD complexes of **8**

| Complex | Solvent | Association constant ($M^{-1}$) |
|---|---|---|
| α-CyD | $H_2O$ | $334 \pm 30$ |
| β-CyD | 30% EtOH | $500 \pm 120$ |

## 3. Supporting information

ROESY and ICD of CyD complexes. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 171239. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: + 44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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18. Whether hydrazine **9** was indeed formed or whether **9** actually represents 4-hydraziadamantan-1-ol cannot be decided at this time.
19. Silica gel 60 (230–400 mesh) and a 7:11 mixture of 0.7 M $NH_{3(MeOH)}$ and EtOAc.
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21. 1.4-Aziadamantan-1-amine (**8**): $\delta_H$ (250 MHz, $CDCl_3$): 0.67 (2H, s), 1.61 (2H, d $^2J$ 13.6 Hz), 1.67 (2H. d $^2J$ 14.8 Hz), 1.70 (2H, s), 1.96 (2H, d $^2J$ 13.6 Hz), 2.01 (2H, d $^2J$ 14.8 Hz), 2.25 (1H, s); $\delta_C$ (63 MHz, $CDCl_3$): 29.5 (t), 34.4 (s), 35.9 (t), 44.1 (s), 45.8 (s), 47.9 (q), (C4 could not be observed); $\nu_{max}/cm^{-1}$ (KBr): 3355, 3265, 2922, 2854, 1575, 1449, 1350, 1293, 1132, 1108, 1067, 926; $m/z$ (FI): 178 ($[M+H]^+$, 100), 165 (64), 149 (92); found: C, 67.61; H, 8.50; N, 23.45%. $C_{10}H_{15}N_3$ requires C, 67.76; H, 8.53; N, 23.71%.
22. Crystal system: monoclinic $P2(1)/n$. **8**: Least-squares refinement on $F^2$ of 260 parameters converged to a final $R_1=0.0310$ for 2994 $F_o>4\sigma$ ($F_o$); (0.0364 for all 3349 values) and a $wR_2=0.0808$.
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30. (a) pH 7.5–8.0; (b) only the association constant for the 1:1 complex can be calculated for the α-CyD complex.