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An expeditious preparation of *E*-2-amino-5-hydroxyadamantane and its *Z*-isomer

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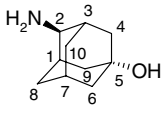
Dedicated to Professor Alajos Kálmán on the occasion of his 70th birthday

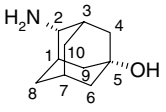
Abstract—Reductive amination of 5-hydroxy-2-adamantanone with *S*-α-methylbenzylamine using 5% Rh–C as the catalyst in the presence of $Al(iOPr)_3$ gave a 3:1 mixture of the *E*- and *Z*-5-hydroxy-adamantane-1-phenethylamines. Choice of catalyst, concentration, solvent and the presence of the hydroxyl group on the adamantane influenced the stereoselectivity of the amination reaction. The desired *E*-isomer could be isolated by fractional crystallization from diisopropyl ether. Debenzylation gave the elusive *E*-2-amino-5-hydroxyadamantane in a 45% overall yield.

There is a growing number of biologically active compounds containing an adamantane moiety. 1-Aminoadamantane (amantadine) and its 3,5-dimethyl analogue memantine are NMDA antagonists with efficacy in preclinical animal models for Parkinson's and Alzheimer's disease. Memantine has been approved for the treatment of Alzheimer's patients.[1] In addition, amantadine, memantine and related aminoadamantanes have a strong activity against influenza A.[2] Adamantane structures are also found in RXR antagonists such as adipalene,[3] squalene synthetase inhibitors,[4] and kinase inhibitors such as adaphostin[5] and $P2X_7$ receptor antagonists.[6] Recently, Novartis and BMS progressed their DPPIV inhibitors vildagliptin[7] and saxagliptin,[8] which contain a 3-hydroxyadamantane moiety, to advanced clinical trials. The 3-hydroxyl group was introduced in the starting adamantane by a simple oxidation of the 1-substituted adamantanes with potassium permanganate[8] or nitric acid.[9]

We needed a quick access to *E*-2-amino-5-hydroxyadamantane **1**,[10] but an exhaustive review of the existing literature did not reveal any practical procedure for the preparation of **1** in preparative useful yields (Fig. 1). It even appeared that neither **1** nor its *Z*-isomer **2** had been obtained in a pure form. Gonzalez-Nunez et al.[11,12] reported the oxidation of 2-aminoadamantane and derivatives with methyl(trifluoromethyl) dioxirane to give a 1:1 mixtures of **1** and **2**, but they were unable to separate the isomers, even as the trifluoroacetamides. Nitration of 2-aminoadamantane gave a mixture of **1** and **2** in a low yield, after hydrolysis of the nitrate esters.[13] Geluk and Schlattmann[14] reported the $LiAlH_4$ reduction of the oxime of commercially available 5-hydroxy-2-adamantanone (which can be prepared by the oxidation of 2-adamantanone with nitric acid[15] or chromic acid[16]) to give a 1:1 ratio of **1** and **2**, which could not be separated at this stage. Similarly, we found that hydrogenation of the oxime or methoxime of 5-hydroxy-2-adamantanone over Raney-nickel also gave a



1 E-2-amino-5-hydroxyadamantane



2 Z-2-amino-5-hydroxyadamantane

Figure 1.

Keywords: Reductive amination; Stereoselective; Heterogeneous catalysis; Adamantane; Stereoisomers.
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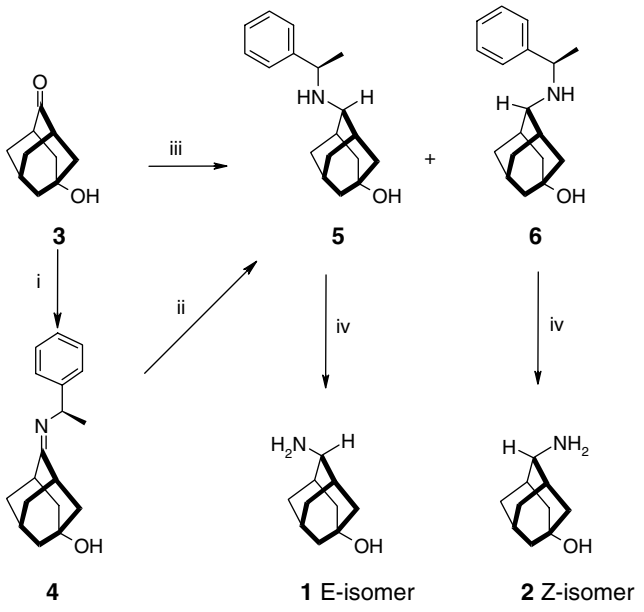
1:1 mixture of **1** and **2**.[17] Lavrova et al. reported the Leuckart reaction of 5-hydroxy-2-adamantanone with formamide and formic acid to give the same 1:1 mixture of **1** and **2**.[18] Some years ago, Johnson et al.[19] described the biooxidation of *N*-benzoyl-2-aminoadamantane to afford the elusive *E*-isomer in a 78% yield as a crystalline substance. According to our knowledge, this is the only method to prepare **1** albeit as its *N*-benzoyl protected form.



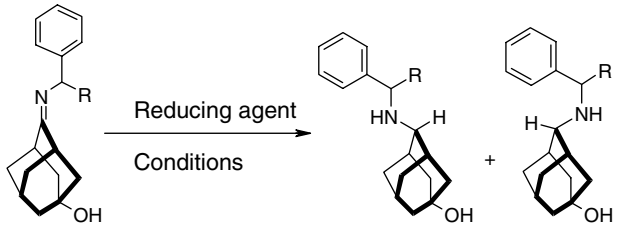
Scheme 1. Reagents and conditions: (i) *S*-α-methylbenzylamine, EtOH, reflux; (ii) H_2, 5% Rh–C, toluene, 50 °C; (iii) *S*-α-methylbenzylamine, H_2, 5% Rh–C, toluene, 50 °C; (iv) H_2, 10% Pd–C, MeOH.

We here report the preparation of **1** and **2** in the pure form for the first time.

LeNoble[20,21] and others[22] have shown that stereoselective reactions on 5-substituted adamantan-2-ones are possible with different degrees of *E*/*Z*-selectivity depending on the 5-substituent. We reasoned that hydrogenation of the imines of 5-hydroxy-2-adamantanone and benzylamines under carefully controlled conditions might lead to an improved ratio of the *E*- and *Z*-isomers, whereby the hydroxyl group would direct the stereoselectivity of the reduction, either through complexation with the catalyst surface or by its hyperconjugation effect.[20–22] Furthermore, the presence of the *N*-benzyl substituent would offer the possibility for an easy HPLC separation, after which it could be removed by a simple hydrogenation.

Indeed, hydrogenation of imine **4** of 5-hydroxy-2-adamantanone and L-*S*-α-methylbenzylamine over Pt–C gave a mixture of the *E*- and *Z*-isomers in a 3.5:1 ratio in a quantitative yield (Scheme 1, Table 1). Separation by preparative HPLC[23] or over silicagel gave the pure isomers **5** and **6**, which were debenzylated under standard conditions to give **1** and **2** in a quantitative yield. Isomers **5** and **6** were identified as *E* and *Z*, respectively, based upon the different NOE correlations of the C2-proton with the neighbouring protons of 4 and 9 for **5** and of 8 and 10 in the case of **6**. The 2D assigned carbon spectra[24] were consistent with the extensive available data on ^{13}C NMR spectra of 2,5-disubstituted adamantanes.[11,25] In the ^1H NMR spectra of **5** and **6**, the position of the C2-proton (2.59 ppm *E*-isomer, 2.45 ppm *Z*-isomer) can be used as an easy diagnostic for the identification of the *E*- and *Z*-isomers.

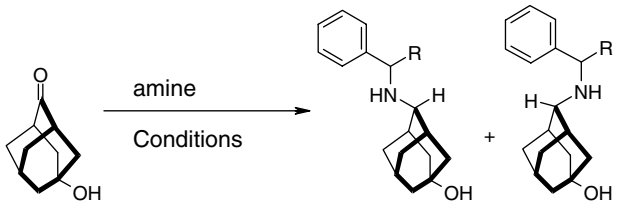
Table 1. Reduction of preformed imines



Entry	R	Red. agent	Solvent	Scale/concn (mmol/M)	Ratio *E*/*Z*[a]
1	*S*-α-Methyl	H_2/5% Pt–C	THF	1/0.025	3.5:1
2	*S*-α-Methyl	H_2/5% Pt–C	THF	56/0.15	1:1
3	*S*-α-Methyl	H_2/RaNi	MeOH	1/0.025	1:1
4	*S*-α-Methyl	H_2/5% Rh–C	THF	14/0.28	1:1
5	*R*-α-Hydroxymethyl	H_2/5% Pt–C	THF	7/0.14	1:1
6	H	H_2/5% Pt–C	THF	10/0.25	1:1
7	*S*-α-Methyl	BH_3	THF	1/0.025	1:1
8	*S*-α-Methyl	$NaBH_4$/HOAc	THF	1/0.025	1:1
9	*S*-α-Methyl	$NaBH_4$/HOAc	THF	1/0.025	1:1
10	*R*-α-Hydroxymethyl	$NaBH_4$/HOAc	THF	1/0.025	1:1

[a] Calculated from the integration of the signals for H-2.

Table 2. Reductive amination of 5-hydroxy-2-adamantanone with different benzylamines using H_2/5% Rh–C (1.6 mol %) and Al(*i*OPr)$_3$. (16 h, 50 °C)



3 E Z

Entry	Amine	Solvent	Scale/concn (mmol/M)	Ratio *E*/*Z*[a]
1	*S*-α-Methylbenzyl	Toluene	10/0.2	3:1
2	*S*-α-Methylbenzyl	Toluene	90/0.6	2:1
3	*S*-α-Methylbenzyl	Toluene	3/0.075	3.3:1
4	*R*-α-Methylbenzyl	Toluene	3/0.075	3.3:1
5	*S*-α-Methylbenzyl	Toluene	10/0.2	4:1[b]
6	*R*/*S*-α-Methylbenzyl	Toluene	3/0.075	3.3:1
7	1-Methylnaphthyl	Toluene	3/0.075	2.3:1
8	Benzyl	Toluene	3/0.075	2.7:1
9	*t*-Butyl	Toluene	3/0.075	3.2:1
10	Dimethylbenzyl	Toluene	3/0.075	No reaction
11	*S*-α-Methylbenzyl	DIPE	3/0.075	2.2:1
12	*S*-α-Methylbenzyl	THF	3/0.075	1.3:1
13	*S*-α-Methylbenzyl	*i*PrOH	3/0.075	1:1
14	*S*-α-Methylbenzyl	MeOH	3/0.075	1:1[c]
15	*S*-α-Methylbenzyl/5-Br	Toluene	3/0.075	1.1:1
16	*S*-α-Methylbenzyl/5-F	Toluene	3/0.075	1.4:1
17	*S*-α-Methylbenzyl/5-OBn	Toluene	3/0.075	1:1

[a] Calculated from the integration of the signals at H-2.
[b] 5 mol % of catalyst.
[c] Complete conversion after 5 days.

Besides experiencing the problem of overreducing the phenyl ring, it proved to be impossible to increase the scale and concentration without losing selectivity completely (entry 2). Hydrogenation of **4** over Raney-Ni or rhodium–C gave a 1:1 mixture of **1** and **2** (entries 3 and 4). Also, hydrogenation of the imines derived from hydroxymethyl benzylamine and benzylamine gave a complete loss of selectivity (entries 5 and 6). Reduction of the imines using borane or sodium borohydride/acetic acid in THF afforded a 1:1 mixture of both isomers (entries 7–10).

It proved to be more convenient to perform the preparation of **5** and **6** via reductive amination of **3** (Scheme 1), thereby circumventing the preparation and isolation of imine **4**. In this case of rhodium on carbon proved to be the catalyst of choice, yielding **5** and **6** in a similar yield and selectivity as observed in the hydrogenation of **4** (Table 2, entry 1). With this method in hand, we studied different alkylarylamines (Table 2). α-Methylbenzylamines proved to give the highest ratios (entries 3, 4 and 6). We did not observe any influence of chirality on the selectivity of the reaction. Substitution on the α-carbon proved to be advantageous for high selectivity, benzyl amine or naphthyl methylamine being significantly less selective (entries 7 and 8). Apparently, the presence of sterically demanding groups is determining for the *E*/*Z* selectivity of the reduction. With *tert*-butylamine a 3.2/1 mixture of *E* and *Z* was obtained (entry 9), but dimethylphenylamine (cumylamine) did not form the imine, even after heating for extended periods of time.

Toluene is clearly superior to ethereal or polar solvents, which may complex with the catalyst surface, thereby decreasing the selectivity (entries 11–14). Also, increasing the concentration lowered the selectivity (entry 2), but increasing the amount of catalyst to 5 mol % increased the selectivity for the *E*-isomer to 4:1 (entry 5). Increasing the amount of amine to 1.8 or 3 equiv also improved the selectivity to about 4:1 (data not shown). The importance of the hydroxyl group in directing the course of hydrogenation is clearly seen in entries 15–17. Replacement of the hydroxyl group with bromine, fluorine or benzyloxy essentially removed the stereoselectivity of hydrogenation.[26]

Upon scaling up to 0.2 mol, under the optimized conditions, reaction of 5-hydroxyadamantan-2-one with *S*-α-methylbenzylamine in the presence of Al(O*i*Pr)$_3$ gave a 3:1 mixture of the adamantyl benzylamines **5** and **6**. Crystallization from diisopropyl ether gave pure benzylamine **5** in a 48% yield. After debenzylation, the desired *E*-2-amino-5-hydroxy-adamantane **1** was obtained in a 45% yield from 5-hydroxy-2-adamantanone **3**.[27] The mother liquor obtained after crystallization of **5** consisted of an approximately 1:1 mixture of **5** and **6**. Debenzylation gave the mixture of amines **1** and **2**, which was oxidized with $KMnO_4$[28,29] to give 5-hydroxy-2-adamantanone.[30]

In conclusion, 5-hydroxy-2-adamantanone **3** can be reductively aminated with good stereoselectivity, giving access to the elusive *E*- and *Z*-2-amino-5-hydroxyadamantanes **1** and **2**.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.056.

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23. Column: Lichroprep amino silicagel. Eluent: EtOAc/heptane 50/50.
24. ^{13}C NMR:

#C	5	6	1	2
1	34.91[a]	35.81[d]	36.80	37.71
2	57.83	57.31	54.32	53.75
3	33.09[a]	34.04[d]	36.80	37.71
4	44.82[b]	39.46[e]	44.78	38.66
5	68.05	67.92	67.56	67.79
6	45.56	45.51	45.60	45.46
7	30.01	30.14	30.27	29.55
8	29.85[c]	35.97[e]	29.25	35.98
9	44.57[b]	39.20[f]	44.78	38.66
10	30.05[c]	35.71[f]	29.25	35.98
CH	55.03	54.69	—	—
Me	24.96	24.97	—	—
Aromatic-q	146.38	146.39	—	—
-ortho	126.51	126.51	—	—
-meta	128.31	128.31	—	—
-para	126.68	126.65	—	—

[a–f] These signals may be mutually interchanged.

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26. In a recent patent (WO2006074244), Patel et al. describe the amination of 4-oxo-adamantane-1-carboxylic acid in 7 M NH_3/MeOH using 5% Pd/C as the catalyst to give an 86% yield of a 13:1 mixture of *E*- and *Z*-4-aminoadamantane-1-carboxylic acid.
27. To a mixture of 5-hydroxy-2-adamantanone (**3**, 33.0 g, 0.2 mol) and *S*-α-methylbenzylamine (25.4 g, 0.21 mol) in dry toluene was added, 40 mL of a 5% solution of thiophene in toluene, Al(O*i*Pr)$_3$ (40.0 g, 0.2 mol) and 5% Rh–C (20 g). With stirring, the mixture was hydrogenated for 16 h at 50 °C. After cooling to room temperature, the catalyst was filtered off, and the filtrate was evaporated till dryness. The residue was taken up in dichloromethane (500 mL), and washed with water (2 × 150 mL). After drying over $MgSO_4$, the organic layer was evaporated to yield an oily residue, which was diluted with diisopropyl ether and set to crystallize. Crystalline **5** was filtered (26 g, 0.095 mol, 48% yield). Compound **5** (23 g, 0.084 mol) was dissolved in MeOH (250 mL), 10% Pd–C (3 g) was added and the mixture was hydrogenated during 16 h. The catalyst was filtered, and the filtrate was evaporated to give **1** (13.5 g, 95%).
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30. Recovery of 5-hydroxy-2-adamantanone: the mother liquor obtained after the crystallization of **5** was evaporated and debenzylated as described for **5** to give a mixture of **1** and **2**. This mixture (7.0 g, 53 mmol) was dissolved in a mixture of water (100 mL), *t*-butanol (150 mL) and 1 M

HCl (60 mL). NaOH (3 M, 40 mL) was added, followed by a mixture of $MgSO_4$ (19.2 g) in 40 mL of water. To this mixture was added dropwise over a period of 1 h, a solution of $KMnO_4$ (22.3 g) in water (350 mL). After stirring for 3 h, solid $NaHSO_3$ was added until a clear solution was obtained. Extraction with dichloromethane (3×100 mL), the organic layers were washed with 1 M HCl, satd $NaHCO_3$ (2×50 mL), dried over $MgSO_4$ and evaporated to give 4.5 g of 5-hydroxy-2-adamantanone **3** (27 mmol, 51%), identical to authentic material.