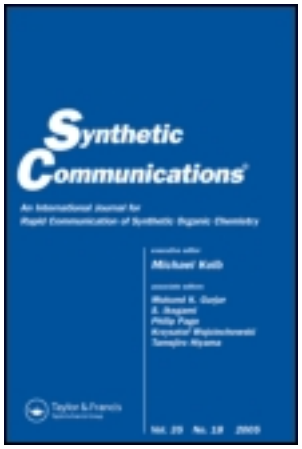

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CONVENIENT SYNTHESIS OF ADAMANTYL-SUBSTITUTED β-LACTAMS VIA UNCATALYZED STAUDINGER REACTION

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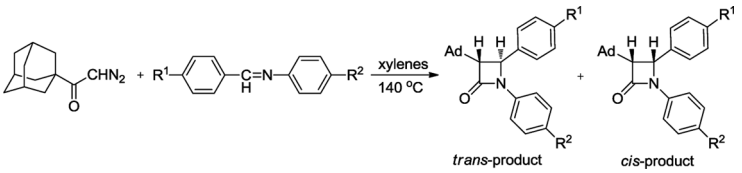
GRAPHICAL ABSTRACT



Abstract *A series of C3-position adamantyl-substituted* β*-lactams were synthesized via uncatalyzed Staudinger reaction between adamantylketene generated by thermal Wolff rearrangement of the corresponding diazo ketone and various imines. The stereochemical outcome of the reaction was mainly the formation of* trans*-products, a result attributed to a two-step mechanism leading to the most stable products.*

Keywords Adamantane; β-lactam; Staudinger reaction; stereoselectivity; thermal Wolff rearrangement

INTRODUCTION

Adamantane possesses a fascinating ring system and has been frequently used in organic reactions because of this unique symmetrical cage structure. Furthermore, its derivatives exhibit significant antiviral, antibacterial, anti-inflammatory, and central nervous system biological activities, so a great number of functionalized molecules containing the adamantyl moiety have been designed and synthesized during recent decades.[1] β-Lactams are an important class of compounds possessing a wide range of antibiotic activities, and for this reason a large number of methodologies

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have been developed for their synthesis.[2] In terms of efficiency and stereochemical predictability, the Staudinger reaction is undoubtedly the most widely used route to β-lactams.[3] Because of the unique structure and potential biological activity of adamantane, we have investigated the combination of the adamantyl moiety with the β-lactam skeleton, as few studies of adamantyl-substituted β-lactams have been reported.[4] Herein, we report a convenient method to synthesize a series of β-lactams substituted at the C3 position by the adamantyl group via uncatalyzed Staudinger reaction between 1-adamantylketene, generated by thermal Wolff rearrangement of the corresponding diazo ketone, with various imines.

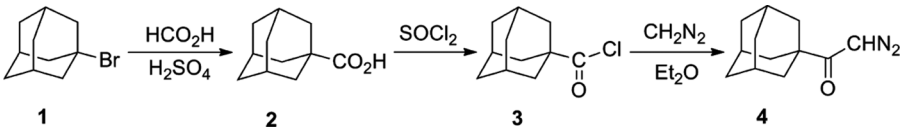
Substituted β-lactams are important compounds that attract research interest for both synthetic and pharmaceutical applications. Their four-membered ring skeleton is difficult to synthesize because of its ring strain.[5] In 1989, Calet and coworkers[4a] prepared a series of 1-(1-adamantyl)-β-lactams from ring expansion of adamantyl-substituted aziridines by rhodium(I)-catalyzed carbonylation. Subsequently, Ohno and coworkers[4b] reported the preparation of the versatile synthetic intermediate 1-adamantyl(ethoxycarbonyl)ketene from the adamantyl-substituted α-diazo-β-oxo ester by photolysis or solution-spray flash vacuum pyrolysis (600 °C) or in the presence of rhodium(II) acetate in dichloromethane. The generated ketene reacted with *N*-benzylidenenamine to yield the 3-(1-adamantyl)-β-lactam.

In this report we describe a convenient method for the preparation of adamantyl-substituted β-lactams using the uncatalyzed thermal Wolff rearrangement, including a study of the stereoselectivity of the reaction.

RESULTS AND DISCUSSION

The uncatalyzed Wolff reaction of 1-diazoacetyladamantane was chosen as the method for the preparation of adamantyl-substituted β-lactams as this offers the distinct advantage in the Staudinger reaction of a clean reaction system without the use of any additives that could affect the *cis*/*trans* ratio of the β-lactam products,[6] and also avoids the possibility of photochemical reaction of the products, which could occur if a light-induced reaction is used. 1-Adamantyl diazo ketone **4** was prepared as shown in Scheme 1. Commercially available 1-bromoadamantane (**1**) was reacted with formic acid at low temperature in sulfuric acid, forming 1-adamantanecarboxylic acid (**2**). 1-Adamantanecarbonyl chloride (**3**), obtained from carboxylic acid **2** under reflux in thionyl chloride, reacted with diazomethane to yield diazo ketone **4** in 85% yield.

Adamantylketene was generated in situ by thermal Wolff rearrangement of diazo ketone **4** in xylenes at 140 °C and reacted in situ with substituted imines **5** by [2 + 2] cycloaddition reaction without catalyst, giving C3-position adamantyl-substituted diastereoisomeric β-lactams **6** (Scheme 2). The yields and stereochemical distribution of the reaction products are shown in Table 1.



Scheme 1. Synthetic route for 1-adamantyl diazo ketone **4** from 1-bromoadamantane (**1**).

Table 1. Stereochemical outcome of [2 + 2] cycloaddition between **4** and **5**

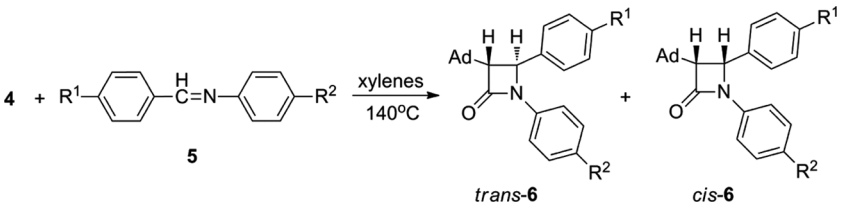
Entry	R^1	R^2	Product	*cis*/*trans*	Yield (%)[a]
1	CH_3O	H	**6a**	0.05:1	67
2	H	CH_3O	**6b**	0.10:1	78
3	H	H	**6c**	0.10:1	82
4	O_2N	CH_3O	**6d**	0.30:1	7
5	O_2N	H	**6e**	0.38:1	51

[a]The isolated yield of *trans*-**6**.

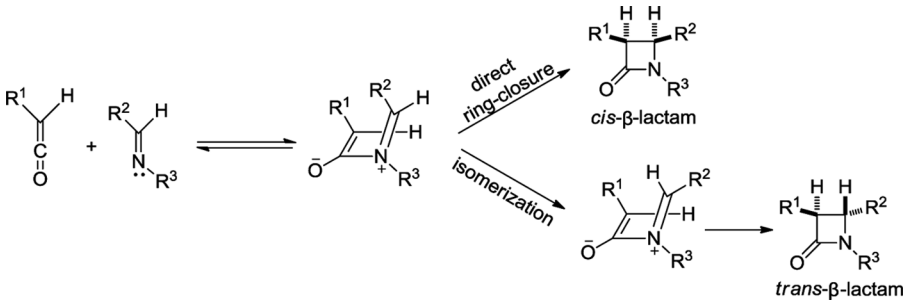
The *cis*- or *trans*-stereochemistry of the β-lactams was established on the basis of their ^{1}H NMR spectra. The coupling constant values for the signals corresponding to the C3 and C4 protons were 6.0–6.4 Hz for the *cis*-isomers and 2.0–2.8 Hz for the *trans*-isomers, in agreement with previously reported values.[7]

As seen in Table 1, the *trans*-products were isolated as the main products of the Staudinger reaction between adamantylketene and various imines. These results can be explained by adamantylketene belonging to the class of ''Moore ketene,'' which possesses the moderately electron-donating adamantyl substituent and has a preference for *trans*-β-lactam formation.[8] Moreover, with the increase of the electron-withdrawing ability of the substituent on the imines, the ratio of *cis*/*trans*-products increased from 0.05:1 to 0.38:1 (entries 1–5). These results indicate that the electron-withdrawing substituent on imines will increase the formation of *cis*-products. The reaction mechanism proposed by Jiao and coworkers can explain our results quite well.[9] They proposed that electron-donating ketene substituents and electron-withdrawing imine substituents accelerate the direct ringclosure, leading to an increased preference for *cis*-β-lactam formation, whereas electron-withdrawing ketene substituents and electron-donating imine substituents slow the direct ring closure, leading to a preference for *trans*-β-lactam formation (Scheme 3).

β-Lactam **6d** prepared from adamantylketene with imine **5d** is formed in poor yield and is difficult to isolate. Surprisingly, amide **11** was obtained as the main product in the reaction conditions. The possible mechanism involves attack of the nitrogen atom of the imine **5d** on the carbonyl carbon of the adamantylketene, forming a zwitterionic intermediate **7**, which undergoes a conrotatory ring closure, leading to the formation of the β-lactam product **6d**. However, the intermediate **7** is highly moisture sensitive and is attacked at the carbon of the imine moiety of **7** by the water existing in the reaction system even in very low concentration to form another zwitterionic intermediate **8**. After the proton transfer from intermediate **8** to enolate



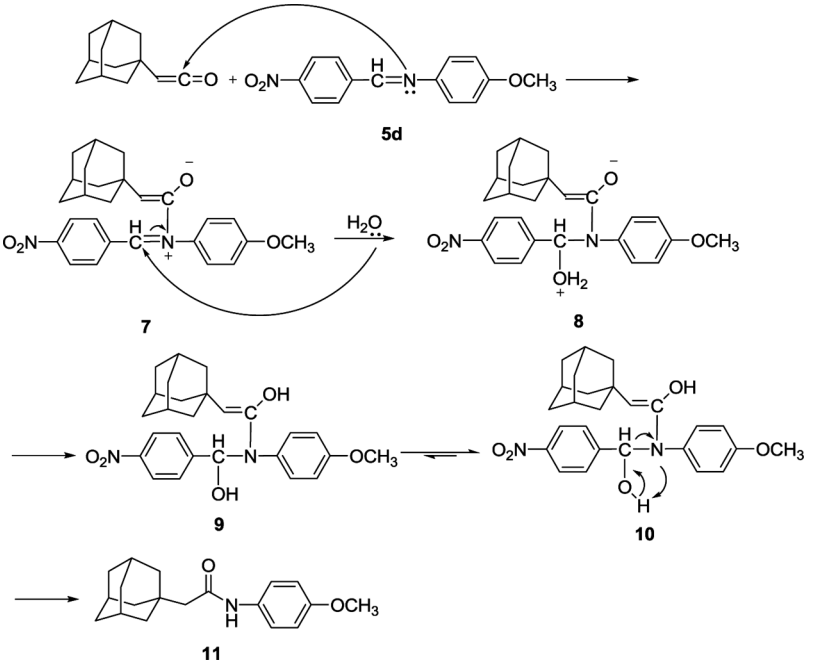
Scheme 2. Preparation of diastereoisomeric β-lactams **6** by [2 + 2] cycloaddition of **4** and **5**.



Scheme 3. Proposed mechanism for the formation of *cis*- and *trans*-β-lactams.

9 and the tautomerization of enolate **9** to ketone **10**, amide **11** is formed by a rearrangement of the unstable ketone **10** with the breaking of C-N bond under the reaction conditions (Scheme 4). However, the possibility that imine was unstable and hydrolyzed to the aniline first, and this reacted with ketene to form amide **11**, cannot be excluded. Similar results have been reported previously.[10,11]

In conclusion, we developed a convenient method to synthesize a series of C3-position adamantyl-substituted β-lactams via uncatalyzed Staudinger reaction between adamantylketene generated by the thermal Wolff rearrangement of the corresponding diazo ketone and various imines. Mainly *trans*-products are formed, a result attributed to a two-stage mechanism proceeding through the least crowded transition state.



Scheme 4. Possible mechanism for the formation of product **11**.

EXPERIMENTAL

Melting points were determined with an Electrothermal X-4 series digital melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 series Fourier transform (FT) IR spectrometer. The NMR spectra were recorded on Bruker Avance 400-MHz spectrometer. The chemical shifts were quoted in parts per million (ppm) in δ values against tetramethylsilane (TMS) as an internal standard, and the coupling constants were calculated in hertz. The low-resolution mass spectra (LRMS) and the high-resolution mass spectra (HRMS) were taken on an Applied Biosystems (Sciex) QStar spectrometer.

Synthesis of 1-Adamantanecarboxylic Acid (2)

A flask charged with 98% concentrated sulfuric acid (125 mL) was stirred in an ice-water bath. 1-Bromoadamantane (**1**) (5.4 g, 25 mmol), hexane (15 mL), and formic acid (15 mL) dropwise were added to it. After 5 h for reaction, the mixture was poured into the ice water (100 mL) and washed with 5% solution of sodium hydroxide. The separated aqueous phase was acidified by concentrated hydrochloric acid (pH 2) and then extracted with chloroform. After removal of solvent under reduced pressure, the residue was obtained as a white solid (5.2 g, 96%).[12]

Synthesis of 2-Diazo-1-(1-adamantyl)-ethanone (4)

Thionyl chloride (3 ml) and 1-adamantanecarboxylic acid (**2**) (1.1 g, 6.1 mmol) were refluxed in benzene (10 ml) at 80 °C for 5 h. Then benzene and excess thionyl chloride was removed in vacuo. After distilling the residual under reduced pressure, a colorless 1-adamantanecarbonyl chloride (**3**) was collected as a liquid. The liquid turned into a white solid quickly at room temperature.

Carbonyl chloride **3** (1.0 g, 5 mmol) in 5 mL ether was added dropwise to a stirred, precooled solution of freshly prepared diazomethane (20 mmol) in 40 mL ether, and then the mixture was stirred in an ice-water bath overnight. The solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel (elution with petroleum ether/ethyl acetate = 4:1 v/v) gave the diazo ketone as yellow solid (0.67 g, 85%). mp 70–72 °C; IR (KBr): 2099 (C=N_2), 1621 (C=O) cm^{-1}.[13]

General Procedure for the Preparation of β-Lactams 6a–e

A flame-dried, three-neck flask was charged with a solution of imine (0.2 mmol) in 10 mL of dry xylenes. The flask was immersed in an oil bath and heated to reflux. A solution of diazo ketone (0.26 mmol) in 5 mL of dry xylenes was then added through a dropping funnel during a period of 10 min. After the addition, the resulting solution was stirred for another 12 h at the same temperature. After removal of the solvent, the residue was purified by flash chromatograghy to remove highly polar impurities. The product mixture was analyzed by ^{1}H NMR spectrum to determine the *cis*/*trans* ratio. Column chromatograghy of the crude mixture on silica gel afforded the corresponding *cis*- and *trans*-β-lactam products.[9]

(±)-*trans*-1-Phenyl-4-methoxyphenyl-3-adamantylazetidin-2-one (*trans*-6a). White solid, yield 67%; mp 155–157 °C; IR (KBr): 1727 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.64–1.85 (m, 12H, Ad-H), 2.03 (s, 3H, Ad-H), 2.81 (d, $J = 2.0$ Hz, 1H, C_3-H), 3.81 (s, 3H, OCH_3), 4.86 (d, $J = 2.4$ Hz, 1H, C_4-H), 6.90 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.03 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.23–7.32 (m, 6H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 34.0, 36.8, 40.0 (C-Ad), 55.0 (OCH_3), 55.3 (C_3-H), 71.8 (C_4-H), 114.5, 116.9, 123.5, 127.2, 129.0, 130.7, 137.7, 159.4 (C-Ar), 166.8 (C=O); ESI-MS: m/z 388.2 ($[M + H]^+$). HRMS (ESI): calcd for $C_{26}H_{30}NO_2$ ($[M + H]^+$): 388.2277; found: 388.2256.

(±)-*cis*-1-Phenyl-4-methoxyphenyl-3-adamantylazetidin-2-one (*cis*-6a). White solid, yield 3%; mp 218–221 °C; IR (KBr): 1741 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.62 (m, 12H, Ad-H), 1.78 (s, 3H, Ad-H), 3.32 (d, $J = 6.0$ Hz, 1H, C_3-H), 3.74 (s, 3H, OCH_3), 5.17 (d, $J = 6.0$ Hz, 1H, C_4-H), 6.78 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.20–7.34 (m, 7H, Ar-H); ESI-MS: m/z 388.2 ($[M + H]^+$).

(±)-*trans*-1-Methoxyphenyl-4-phenyl-3-adamantylazetidin-2-one (*trans*-6b). White solid, yield 78%; mp 173–175 °C; IR (KBr): 1726 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.68–1.85 (m, 12H, Ad-H), 2.04 (s, 3H, Ad-H), 2.81 (d, $J = 2.4$ Hz, 1H, C_3-H), 3.75 (s, 3H, OCH_3), 4.85 (d, $J = 2.4$ Hz, 1H, C_4-H), 6.79 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.24 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.28–7.39 (m, 5H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 34.0, 36.8, 40.0 (C-Ad), 55.4 (OCH_3), 59.1 (C_3-H), 71.8 (C_4-H), 114.3, 118.1, 126.0, 128.0, 129.1, 131.3, 138.9, 155.8 (C-Ar), 166.1 (C=O); ESI-MS: m/z 388.2 ($[M + H]^+$); HRMS (ESI): calcd for $C_{26}H_{30}NO_2$ ($[M + H]^+$): 388.2277; found: 388.2260.

(±)-*cis*-1-Methoxyphenyl-4-phenyl-3-adamantylazetidin-2-one (*cis*-6b). White solid, yield 7%; mp 232–233 °C; IR (KBr): 1742 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.65 (m, 12H, Ad-H), 1.78 (s, 3H, Ad-H), 3.32 (d, $J = 6.0$ Hz, 1H, C_3-H), 3.75 (s, 3H, OCH_3), 5.17 (d, $J = 6.0$ Hz, 1H, C_4-H), 6.78 (d, $J = 9.2$ Hz, 2H, Ar-H), 7.21 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.30–7.34 (m, 5H, Ar-H); ESI-MS: m/z 388.2 ($[M + H]^+$).

(±)-*trans*-1-Phenyl-4-phenyl-3-adamantylazetidin-2-one (*trans*-6c). White solid, yield 82%; mp 194–195 °C; IR (KBr): 1731 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.69–1.86 (m, 12H, Ad-H), 2.04 (s, 3H, Ad-H), 2.83 (d, $J = 2.8$ Hz, 1H, C_3-H), 4.90 (d, $J = 2.4$ Hz, 1H, C_4-H), 7.04 (t, $J = 7.2$ Hz, 1H, Ar-H), 7.23–7.39 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 34.1, 36.8, 40.0 (C-Ad), 55.4 (C_3-H), 71.8 (C_4-H), 116.9, 123.6, 126.0, 128.1, 129.0, 129.1, 137.6, 138.8 (C-Ar), 166.6 (C=O); ESI-MS: m/z 358.2 ($[M + H]^+$). HRMS (ESI): calcd for $C_{25}H_{28}NO$ ($[M + H]^+$): 358.2171; found: 358.2154.

(±)-*cis*-1-Phenyl-4-phenyl-3-adamantylazetidin-2-one (*cis*-6c). White solid, yield 8%; mp 214–216 °C; IR (KBr): 1741 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.65 (m, 12H, Ad-H), 1.79 (s, 3H, Ad-H), 3.34 (d, $J = 6.4$ Hz, 1H, C_3-H), 5.22 (d, $J = 6.0$ Hz, 1H, C_4-H), 7.03 (m, 1H, Ar-H), 7.22–7.36 (m, 9H, Ar-H); ESI-MS: m/z 358.2 ($[M + H]^+$).

(±)-*trans*-1-Nitrophenyl-4-methoxyphenyl-3-adamantylazetidin-2-one (*trans*-6d). White solid, yield 7%; mp 148–151 °C; IR (KBr): 1726 (C=O) cm^{-1}; ^1H

NMR (400 MHz, $CDCl_3$): δ 1.66–1.83 (m, 12H, Ad-H), 2.04 (s, 3H, Ad-H), 2.78 (d, $J = 2.4$ Hz, 1H, C_3-H), 3.74 (s, 3H, OCH_3), 4.93 (d, $J = 2.0$ Hz, 1H, C_4-H), 6.79 (d, $J = 9.2$ Hz, 2H, Ar-H), 7.17 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.50 (d, $J = 8.8$ Hz, 2H, Ar-H), 8.22 (d, $J = 8.8$ Hz, 2H, Ar-H); ESI-MS: m/z 433.2 ($[M + H]^+$); HRMS (ESI): calcd for $C_{26}H_{29}N_2O_4$($[M + H]^+$): 433.2127, found: 433.2139.

(±)-*cis*-1-Nitrophenyl-4-methoxyphenyl-3-adamantylazetidin-2-one (*cis*-6d). White solid, yield 3%; mp 217–220 °C; IR (KBr): 1744 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.63 (m, 12H, Ad-H), 1.81 (s, 3H, Ad-H), 3.44 (d, $J = 6.4$ Hz, 1H, C_3-H), 3.75 (s, 3H, OCH_3), 5.24 (d, $J = 6.0$ Hz, 1H, C_4-H), 6.80 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.14 (d, $J = 9.2$ Hz, 2H, Ar-H), 7.56 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.21 (d, $J = 7.2$ Hz, 2H, Ar-H); ESI-MS: m/z 433.2 ($[M + H]^+$).

(±)-*trans*-1-Phenyl-4-nitrophenyl-3-adamantylazetidin-2-one (*trans*-6e). White solid, yield 51%; mp 254–256 °C; IR (KBr): 1737 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.67–1.84 (m, 12H, Ad-H), 2.04 (s, 3H, Ad-H), 2.80 (d, $J = 2.0$ Hz, 1H, C_3-H), 4.98 (d, $J = 2.0$ Hz, 1H, C_4-H), 7.05 (t, $J = 6.8$ Hz, 1H, Ar-H), 7.22–7.28 (m, 4H, Ar-H), 7.51 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.22 (d, $J = 8.4$ Hz, Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1, 34.3, 36.7, 40.1 (C-Ad), 54.6 (C_3-H), 72.2 (C_4-H), 116.7, 124.1, 124.5, 126.9, 129.3, 137.1, 146.5, 147.8 (C-Ar), 165.6 (C=O); ESI-MS: m/z 403.2 ($[M + H]^+$). HRMS (ESI): calcd. for $C_{25}H_{27}N_2O_3$ ($[M + H]^+$): 403.2022; found: 403.2029.

(±)-*cis*-1-Phenyl-4-nitrophenyl-3-adamantylazetidin-2-one (*cis*-6e). White solid, yield 18%; mp 189–191 °C; IR (KBr): 1748 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.41–1.64 (m, 12H, Ad-H), 1.82 (s, 3H, Ad-H), 3.46 (d, $J = 6.4$ Hz, 1H, C_3-H), 5.29 (d, $J = 6.4$ Hz, 1H, C_4-H), 7.07 (t, $J = 7.6$ Hz, 1H, Ar-H), 7.19 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.24–7.28 (m, 2H, Ar-H), 7.58 (s, br, 2H, Ar-H), 8.21 (s, br, 2H, Ar-H); ESI-MS: m/z 403.2 ($[M + H]^+$).

N-(4-Methoxyphenyl)-1-adamantylacetamide (11)

White solid, yield 64%; mp 164–165 °C; IR (KBr): 1652 (O=C-NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.63–1.73 (m, 12H, Ad-H), 1.99 (s, 3H, Ad-H), 2.07 (s, 2H, CH_2C=O), 3.79 (s, 3H, OCH_3), 6.85 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.99 (s, 1H, N-H), 7.41 (d, $J = 8.8$ Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.6, 33.3, 36.7, 42.7 (C-Ad), 52.7 (CH_2), 55.5 (OCH_3), 114.1, 121.8, 131.0, 156.4 (C-Ar), 169.2 (C=O); ESI-MS: m/z 300.1 ($[M + H]^+$).

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