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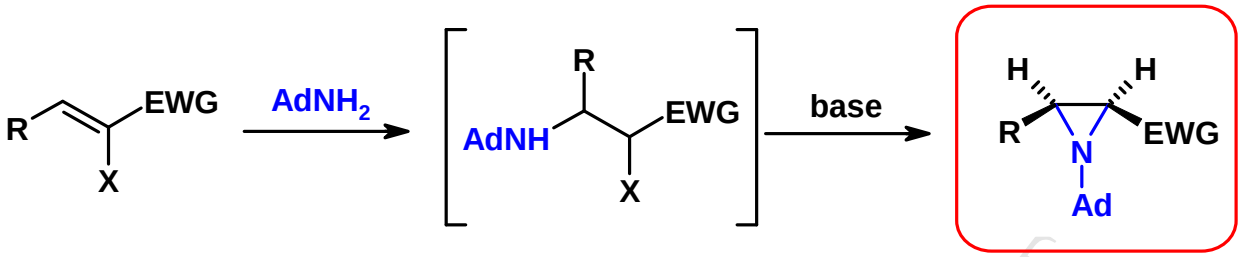
Graphical Abstract



Adamantyl aziridines via aza-Michael initiated ring closure (aza-MIRC) reaction

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Abstract

An efficient one-pot synthesis of functionalized adamantylaziridines by aza-Michael initiated ring closure (aza-MIRC) reaction of 1-aminoadamantane with α-halogenated Michael acceptors is described. The reaction goes through an aza-Michael intermediate that undergoes an intramolecular nucleophilic substitution. Expectedly, high pressure exerts a beneficial influence in the case of sterically hindered reagents.

Keywords: aza-Michael addition, aziridines, aminoadamantane

Introduction

Nitrogen-bearing heterocycles are structural fragments found in a large variety of natural products and drugs, explaining why they are regarded as privileged pharmacophores. Aziridines are no exception and possess pronounced biological activities such as antibacterial, anti-inflammatory and cytostatic properties have been evidenced for structures exhibiting this pattern. These three-membered aza-heterocyclic systems are also known to undergo relatively facile ring opening, a reaction that can pave new routes toward complex polyfunctional natural and biologically active compounds.[1,2]

On the other hand the adamantyl moiety, and in particular the 1-aminoadamantane (amantadine), is found in several modern drugs[3] possessing anti-viral[4] and anti-diabetic[5] properties, generally mediated by their channel-blocking activities.[6] Those are also used for treating neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.[7] Therefore, one can expect that the fragment-based combination of adamantane and aziridine moieties would provide derivatives exhibiting new biological activities.

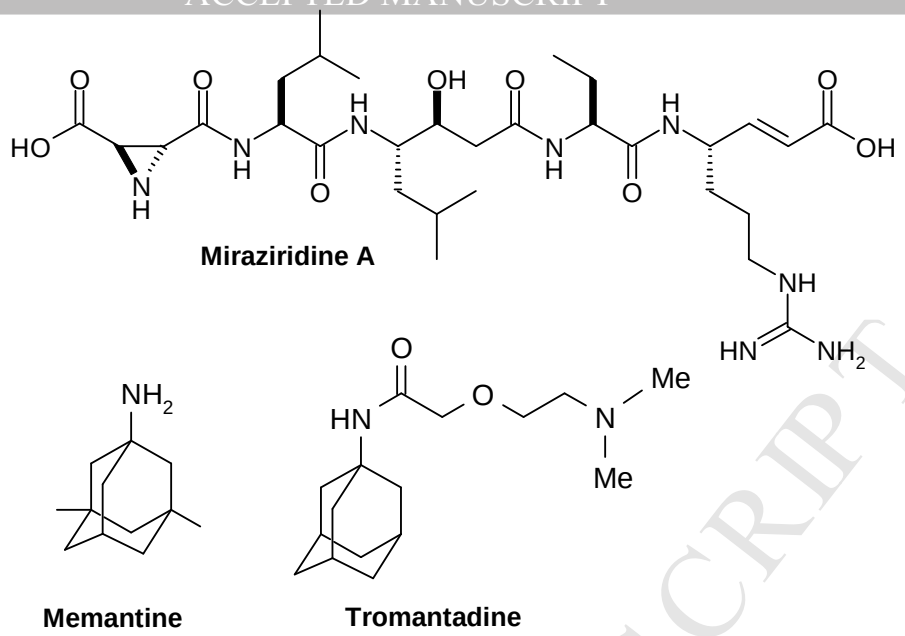
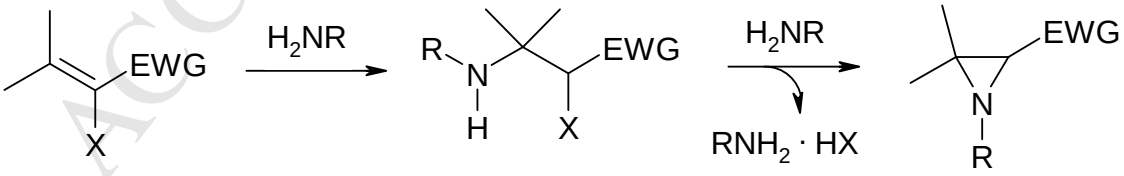


Figure 1. Some 1-aminoadamantane and aziridine-derived bioactive compounds.

The potential displayed by these pharmacophores prompted us to explore new routes toward compounds bearing both the aminoadamantyl and aziridine moieties. To the best of our knowledge, only one approach to such derivatives has been reported by *Johnston* and co-authors who showed that the addition of electron-rich azides including adamantyl azide to methyl vinyl ketone gives acetyl aziridines in good yield under relatively mild conditions.[8] One of the most convenient and general ways toward aziridine derivatives is the domino-reaction of primary amines as 1,1-binucleophiles with activated olefins containing a good leaving group at the α-position. In this case, an aza-Michael reaction takes place,[9] immediately followed by a cyclization triggered by an intramolecular nucleophilic substitution (Scheme 1).

Scheme 1. Domino-assembly of the aziridine core



However, such a strategy does not seem to be appropriate when it comes to adamantylamine that can be regarded as an exceptionally bulky nucleophile. Herein, we describe the synthesis of adamantylaziridine derivatives based on the addition of 1-aminoadamantane onto various halogen-bearing Michael acceptors.

Results and discussion

The simplest access to the target compounds could thus be a tandem sequence involving a conjugate nucleophilic addition of aminoadamantane followed by an intramolecular substitution of a halogen leaving group. However, reaction of a very cumbersome nucleophile with Michael acceptors bearing substituents in the α and/or β positions could appear mostly unrealistic since the aza-Michael reaction is known to be hampered by such substitution patterns.[9-12] We thus first examined the reaction of 1-aminoadamantane with several non-halogenated Michael acceptors, supposed to be more responsive partners.

Indeed, the activated alkenes **1a-c** containing a terminal double bond react readily with 1-aminoadamantane to give the expected adducts **2a-c** (Table 1, entries 1-3). The nature of the activating group does not affect the selectivity and efficiency of the addition process: in all cases the reaction proceeds at room temperature and results in the formation of the 1,4-adducts in high yields.

Table 1. Conjugate addition of 1-aminoadamantane to Michael acceptors

1a-f **2a-d**

Entry	Michael acceptor				Conditions	Product, (Yield, %)[a]
		R^1	R^2	EWG		
1	**1a**	H	H	CO_2Me	rt, 17 h	**2a** (79)
2	**1b**	H	H	CN	rt, 17 h	**2b** (82)
3	**1c**	H	H	SO_2Ph	rt, 17 h	**2c** (92)
4	**1d**	Me	H	CO_2Me	rfx, 17 h	0
5	**1d**	Me	H	CO_2Me	rt, 10 kbar, 17 h	**2d** (28)
6	**1e**	Me	Me	CO_2Me	rt, 10 kbar, 24 h	traces [b]
7	**1f**	Ph	H	C(O)Me	rt, 10 kbar, 24 h	0

[a] Isolated yield. [b] Starting ester **1e** was recovered only.

Unlike methyl acrylate **1a**, the homologous methyl crotonate **1d**, bearing an internal double bond, does not react with 1-aminoadamantane under classical conditions and the starting materials were recovered after reflux in methanol for 17 hours. High pressure (>10 kbar) is known to overcome the lack of reactivity of sterically hindered substrates, particularly for this addition reaction.[10,11] Expectedly, the hyperbaric (10 kbar) reaction of aminoadamantane with methyl crotonate **1d** proceeds at room temperature and gives adduct **2d**, however in a low 28% yield (Table 1, entry 5). This result remains worth noting since it provides a particularly bulky

secondary amine surrounded by quaternary and tertiary substituents. Unfortunately, the incorporation of a second methyl group at the β-position (methyl senecioate **1e**) or the presence of a terminal aromatic substituent (benzylideneacetone **1f**) prevents the amine addition, even under high pressure (Table 1, entries 6, 7).

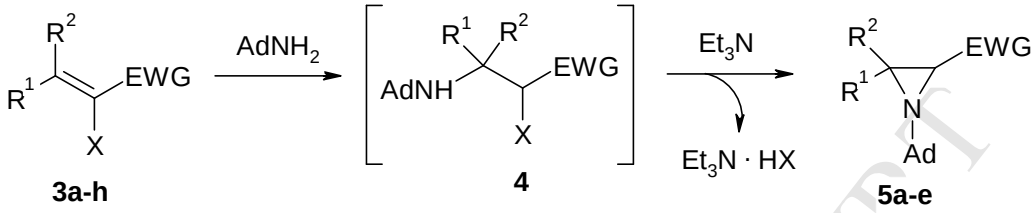
We further pursued this study resorting to halogenated electron-deficient alkenes **3**. In this case, the presence of a chloro or a bromo atom in the α-position increases the electrophilicity of the *β*-sp^2 carbon atom and is, therefore, expected to favor the conjugate addition. Moreover, these halides behave as good leaving groups and are thus anticipated to favor the intramolecular nucleophilic substitution.

Initial experiments were run at atmospheric pressure. We observed that 1-aminoadamantane, similarly to other primary amines, adds efficiently to the halogenated activated terminal double bond in **3a-c**. Thus, the alkenes bearing methoxycarbonyl (**3a**), acetyl (**3c**), or cyano group (**3b**) gave the target aziridines **5a-c** in high yields, however the presence of additional base was required (Et_3N: Table 2, entries 1-3). The reaction proceeds easily in protic solvents at room temperature. In contrast to substrates **3a-c**, the reaction of bromosulfone **3d** with the amine stops at the aza-Michael adduct **4** (Table 2, entry 4), and all attempts to perform the ring-closure reaction in a separate step failed in this case.

To our delight, methyl *α*-chlorocrotonate **3e** gives the expected aziridine **5d** in good yield under classical conditions, similarly to unsubstituted acrylates (Table 2, entry 5). The use of bromine, that has a much weaker electron withdrawing effect and a higher steric hindrance than chlorine, results in a substantial decrease of reactivity: 1-aminoadamantane does not add to methyl *α*-bromocrotonate **3f** under the conditions used for terminal alkenes (Table 2, entry 7). It was shown earlier that the hyperbaric synthesis of aziridinecarboxylates is easily carried out from *β,β*-disubstituted bromoacrylates provided that the amines are sufficiently basic and their nitrogen atom is sterically available.[10] Comparably, the treatment of methyl *α*-bromocrotonate **3f** with adamantylamine under 6 kbar forms aziridine **5d** (Table 2, entry 6), as a single syn-diastereomer (*vide infra*). The moderate yield (44%) of aziridinecarboxylate in this case can be explained by the occurrence of the competitive oxa-Michael addition of methanol (used as solvent), giving adduct **6a** in 32% yield (Scheme 2). Attempts to avoid this side reaction by replacing methanol (or ethanol) by non-nucleophilic alcohols (isopropanol or *tert*-butanol) remained unsuccessful due to the low solubility of the initial amine in these solvents. Pleasingly, the 3-bromo-4-phenylbut-3-ene-2-one **3g**, absolutely inactive toward amine **1** under classical conditions, gives, under high pressure, aziridine **5e** (39% yield, again as a single syn-diastereomer) along with 12% of oxa-adduct **6b** (Table 2, entries 8, 9; Scheme 2). NMR spectra

of the crude mixtures suggest that **6a**,**b** are formed as an almost equimolar mixture of diasteromers.

Table 2. Aziridination of Michael acceptors with 1-aminoadamantane

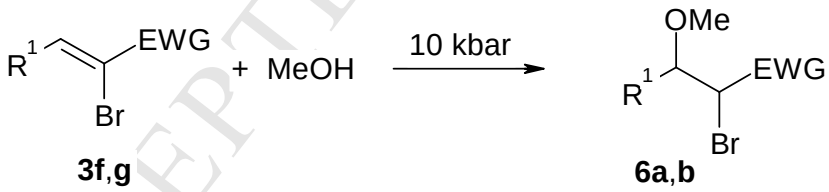


3a-h **4** **5a-e**

Entry	Michael acceptor	R^1	R^2	X	EWG	Conditions [a]	Product (yield,%) [b]
1	**3a**	H	H	Cl	CO_2Me	MeOH, Et_3N, rt	**5a** (67)
2	**3b**	H	H	Cl	CN	EtOH, Et_3N, rt	**5b** (58)
3	**3c**	H	H	Br	C(O)Me	MeOH, Et_3N, rt	**5c** (82)
4	**3d**	H	H	Br	SO_2Ph	EtOH, Et_3N, rt	**4** (81)
5	**3e**	Me	H	Cl	CO_2Me	MeOH, Et_3N, rt	**5d** (67)
6	**3f**	Me	H	Br	CO_2Me	MeOH, Et_3N, rt, 6 kbar	**5d** (44) + **6a** (32)
7	**3f**	Me	H	Br	CO_2Me	EtOH, Et_3N, rt	no reaction
8	**3g**	Ph	H	Br	C(O)Me	MeOH, rt, 10 kbar	**5e** (39) + **6b** (12)
9	**3g**	Ph	H	Br	C(O)Me	MeOH, Et_3N, rfx	no reaction
10	**3h**	Me	Me	Br	CO_2Et	EtOH, rt, 10 kbar [c]	**7** (38)

[a] The reaction time is 17 h; [b] Isolated yield; [c] The reaction time is 24 h.

Scheme 2. Competitive oxa-Michael reaction

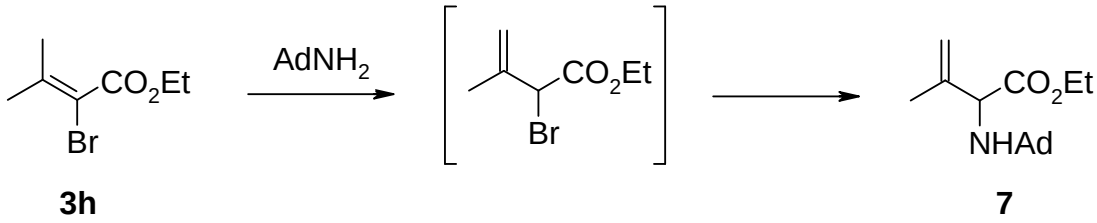


3f,**g** **6a**,**b**

6: R^1 = Me, EWG = CO_2Me (**a**);
R^1 = Ph, EWG = C(O)Me (**b**)

Finally, we carried out the reaction of *β*,*β*-disubstituted bromoacrylate **3h** with 1-aminoadamantane. To avoid the transesterification process ethanol was used as solvent. But the only isolated product turned out to be enoate **7** (38% yield). Its formation can be easily explained by an initial double bond migration and subsequent substitution of the allylic bromine (Scheme 3). Similar transformations proceeding in the presence of strong bases are well known.[13] One can speculate that the increase of acidity of the methyl allylic protons under high pressure triggers the double bond migration under the influence of adamantylamine.

Scheme 3. Reaction of 2-bromo-3-methyl butenoate **3h** with 1-aminoadamantane



3h **7**

The ^{1}H NMR spectra of aziridines **5a-e** exhibit the sharp, well-resolved, signals of three-membered ring. Thus, the ^{3}J constants of all aziridine protons could be measured with accuracy. Completed with 2D (NOESY) NMR spectra of **5a-c**, these data allowed us to determine unambiguously the relative configuration between protons 2 and 3. The ^{3}J for *cis*-aziridine ring protons reach 6.2-6.6 Hz while these values are known to be in the 2.6-2.8 Hz range for *trans*-2,3-protons.[14] On these bases, the 2,3-*cis* configuration was assigned to aziridines **5d**,**e**. Moreover, we have measured the direct coupling constants ^{1}J(CH) for both methine and methylene aziridine groups running 2D HSQC experiments. Indeed, these values display pronounced stereospecific dependence on the nitrogen lone pair arrangement.[15] Typically, the difference between the ^{1}J (CH) values for the CH_2 moiety reaches 13-15 Hz: the ^{1}J (CH) values for the *cis*- and *trans*-protons belonging to the methylene group of aziridine **5a** are 179.7 and 165.4 Hz, respectively. This result comes to fully support our conclusions on the stereochemistry of the aziridines **5** (Figure 2).

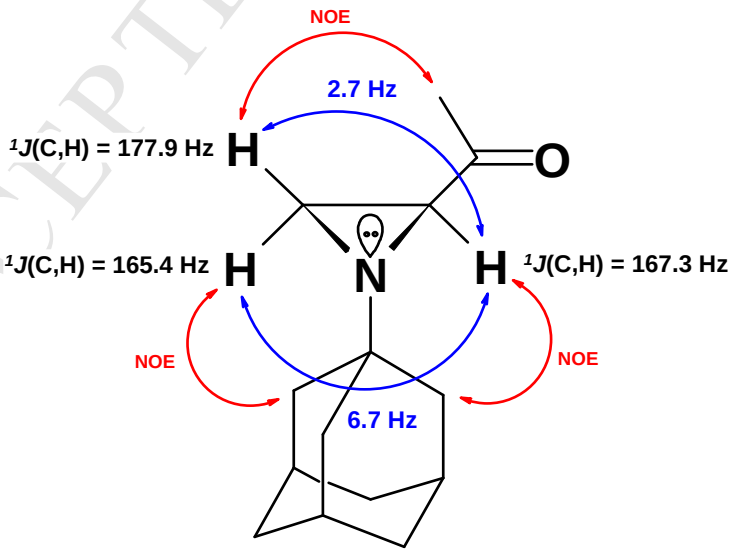
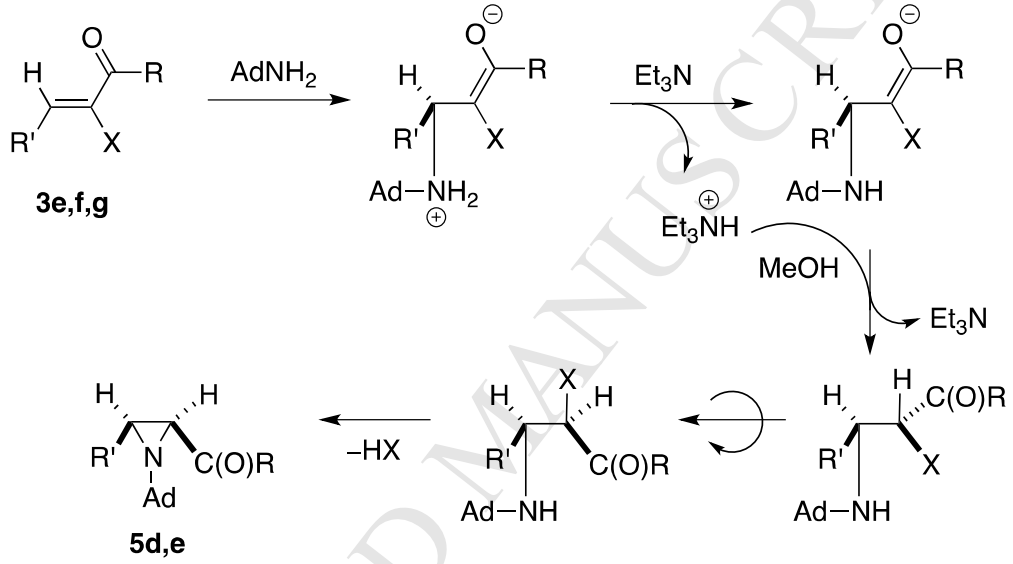


Figure 2. Key NOE interactions and coupling constants for compound **5c**

This stereospecificity suggests that the protonation of the aza-Michael enolate intermediate occurs in an intermolecular fashion. We believe that the ammonium resulting directly from the addition is deprotonated by the triethylamine in the medium and that the resulting Et_3NH^+ acts in turn as the protonating agent for the enolate. These preliminary steps are then followed by a rotation putting the leaving group *anti* to the amino appendage, allowing the final formation of aziridines **5** by an intramolecular S_N2 that accounts for the observed stereoselectivity (Scheme 4).

Scheme 4. Stereoselective formation of the aziridines **5**



Finally, aziridines, by contrast to other cyclic amines, usually exhibit a barrier to nitrogen inversion. Therefore, *a priori* the target aziridines can exist as a mixture of two invertomers.[16] In this case, the large low-resolved signals of both invertomers in solution at room temperature should be observed in both ^1H and ^{13}C NMR spectra. Only sharp signals were observed in the NMR spectra of adamantylaziridines **5** suggesting the absence of this inversion due to the presence of the bulky *N*-substituent, acting as a conformational anchor.

In conclusion, we have shown that the aza-Michael addition, under both classical and hyperbaric conditions, followed by intramolecular nucleophilic substitution, allows an efficient and facile access to adamantylaziridines in one step from adamantylamine and standard *α*-halogenated Michael acceptors. The reaction proceeds at room temperature, without catalyst, leading to the expected heterocycles in good yields. The high-pressure activation reveals itself, once more here, as a precious tool to overcome the adverse effect of bulkiness in the aza-Michael addition.

Experimental

General remarks. ^{1}H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker AVANCE 400 MHz (at 400, 100, and 40 MHz, respectively) and Bruker AVANCE 300 MHz (at 300 and 75 MHz, respectively) spectrometers for solution in $CDCl_3$. Chemical shifts (δ) in ppm are reported using residual chloroform (7.24 for ^{1}H and 77.2 for ^{13}C) as internal reference. The coupling constants (J) are given in Hertz. The concerted application of ^{1}H-^{1}H 2D homonuclear experiments COSY and NOESY as well as ^{1}H-^{13}C 2D heteronuclear experiments HSQC and HMBC were used for the distinction of the carbon and proton resonances in all cases. The IR spectra were measured with Bruker Vertex 70 FT-IR and portable Varian 3100 diamond ATR/FT-IR instruments. The GC/MS analyses were performed on a Hewlett-Packard HP 5971A instrument (EI, 70 eV). The silica gel used for flash chromatography was 230-400 Mesh. All reagents were of reagent grade and were used as such or distilled prior to use. All the solvents were dried according to standard procedures and freshly distilled prior to use. Haloderivatives **3a**,**b** are commercial. 3-Bromobut-3-ene-2-one **3c** was prepared as reported previously.[17] Bromovinyl phenyl sulfone **3d** was prepared according to the known procedure.[18]

General procedure for the reaction of Michael acceptors (1a-c) with adamantylamine

The mixture of 1-aminoadamantane (151 mg, 1 mmol) and Michael acceptor (**1a-c**) (2 mmol) in solvent (2 mL) was stirred at room temperature for 17 h. The crude product was purified by column chromatography (Silica gel, chloroform/methanol 9/1 (for **2a**,**c**); and 95/5 (for **2b**)). The following compounds were prepared according to this procedure.

Methyl 3-(adamantan-1-ylamino)propionate 2a. Yellow oil (187 mg, 79%) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.25 (br.s, 1H, NH), 1.48-1.60 (m, 12H, Ad), 1.98-2.05 (m, 3H, Ad), 2.42 (t, J = 6.0 Hz, 2H, CH_2CO), 2.80 (t, J = 6.0 Hz, 2H, CH_2N), 3.61 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.6, 36.8, 42.7, 50.4 (Ad), 35.7 ($\underline{C}H_2CO$), 36.0 (CH_2N), 51.5 (CH_3), 173.4 (C=O). IR (cm^{-1}): ν 1738 (C=O), 3317 (NH). HRMS (ESI, m/z) calcd for $C_{14}H_{23}NO_2$ 237.1729; found 237.1728.

3-(Adamantan-1-ylamino)propionitrile 2b. White solid (168 mg, 82%). m.p. = 48 ºC. Lit.:[7a] 48 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (br.s, 1H, NH), 1.50-1.70 (m, 12H, Ad), 2.01 (br.s, 3H, Ad), 2.40 (t, J = 6.8 Hz, 2H, CH_2CN), 2.83 (t, J = 6.8 Hz, 2H, CH_2N); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3 ($\underline{C}H_2CN$), 29.5, 36.6, 42.8, 50.7 (Ad), 36.8 (CH_2N), 119.0 (CN). IR (cm^{-1}): ν 2247 (CN), 3310 (NH). MS (EI) *m/z* (relative intensity): m/z (%): 204 (17, M^+), 164 (50), 147 (69), 135 (62), 106 (100), 79 (21). Calcd for $C_{13}H_{20}N_2$: C 76.42; H 9.87; N 13.71. Found: C 76.46; H 9.87; N 13.81.

Adamantan-1-yl-(2-benzenesulfonylethyl)amine 2c. Colorless oil (294 mg, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (br.s, 1H, NH), 1.50-1.68 (m, 12H, Ad), 1.98-2.05 (m, 3H, Ad), 2.87-3.00 (m, 2H, CH_2N), 3.12-3.37 (m, 2H, CH_2SO_2), 7.42-7.50 (m, 2H, Ar), 7.60-7.68 (m, 1H, Ar), 7.85-7.95 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.6, 36.7, 42.6, 50.8 (Ad), 34.6 (CH_2N), 57.6 (CH_2SO_2), 128.1, 129.4, 133.8, 139.6 (Ph). IR (cm^{-1}): *v* 1143, 1307 (SO_2), 3317 (NH). MS (EI) *m/z* (relative intensity): m/z (%): 319 (6, M^+), 263 (24), 262 (100), 177 (67), 135 (57), 120 (82), 93 (46), 77 (74). Calcd for $C_{18}H_{25}NO_2S$: C 67.68; H 7.89; N 4.38; S 10.04. Found: C 67.44; H 7.90; N 4.31, S 9.78.

Methyl 3-(adamantan-1-ylamino)butanoate 2d: The mixture of aminoadamantane (151 mg, 1 mmol), and methyl crotonate (200 mg, 2 mmol) in methanol (1.0 mL) was placed in a Teflon reaction vessel and pressurized to 10 kbar at room temperature for 17 h. After that, the pressure was released and the mixture was concentrated *in vacuo*. The crude product **2d** was purified by column chromatography (Silica gel, eluent Ether). Colorless oil (70 mg, 28%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.97 (br.s, 1H, NH), 1.08 (d, J = 6.4 Hz, 3H, CH_3C), 1.50-1.63 (m, 12H, Ad), 1.98-2.03 (m, 3H, Ad), 2.26 (dd, J = 15.1, 6.1 Hz, 1H, CH_2), 2.36 (dd, J = 15.1, 6.4 Hz, 1H, CH_2), 3.24-3.35 (m, 1H, CH), 3.63 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.0 (CH_3), 29.8, 36.8, 43.2, 51.2 (Ad), 43.2 (CH_2), 45.3 (CH), 51.5 (CH_3O), 173.0 (C=O). IR (cm^{-1}): *v* 1732 (C=O), 3319 (NH). HRMS (ESI, m/z) calcd for $C_{15}H_{26}NO_2$ 252.1964; found 252.1962.

General procedure for the synthesis of aziridines (5a-f) and aza-adduct 4:

Under classical conditions. The mixture of 1-aminoadamantane (151 mg, 1 mmol), Michael acceptor (**3a-e**) (2 mmol), and triethylamine (111 mg, 1.1 mmol) in the corresponding solvent (2 mL) was stirred at room temperature for 17 h. Then the mixture was concentrated *in vacuo*. The crude product was purified by column chromatography (Silica gel, chloroform/methanol 98/2 (for **4**); 9/1 (for **5a**), 95/5 (for **5c**), ether (for **5d**); or Al_2O_3, chloroform (for **5b**)). The following compounds were prepared according to this procedure.

Methyl (1-adamantan-1-yl)aziridine-2-carboxylate 5a. Light yellow oil (158 mg, 67%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.40-1.60 (m, 12H, Ad), 1.86 (dd, J = 2.8, 1.3 Hz, 1H, CH_2), 1.92 (dd, J = 6.3, 1.3 Hz, 1H, CH_2), 1.97-2.05 (m, 3H, Ad), 2.39 (dd, J = 6.3, 2.8 Hz, 1H, CH), 3.65 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.2 (CH_2), 28.9 (CH), 29.4, 36.6, 40.0, 53.5 (Ad), 52.2 (CH_3), 172.5 (C=O); ^{15}N NMR ($CDCl_3$, 40 MHz): δ -332.4. IR (cm^{-1}): *v* 1732 (C=O). MS (EI) *m/z* (relative intensity): m/z (%): 235 (7, M^+), 136 (12), 135 (100), 107 (15), 93 (23), 79 (28), 41 (21). Calcd for $C_{14}H_{21}NO_2$: C 71.46; H 8.99; N 5.95. Found: C 71.49; H 8.94; N 5.97.

(1-Adamantan-1-yl)-aziridine-2-carbonitrile 5b. White solid (119 mg, 58%), m.p. 48-49 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.40-1.69 (m, 12H, Ad), 1.95-2.05 (m, 2H, CH_2), 2.02-2.10 (m, 3H, Ad), 2.24-2.29 (m, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.5 (CH_2), 26.4 (CH), 29.4, 36.5, 39.8, 53.8 (Ad), 119.9 (CN). IR (cm^{-1}): *v* 2245 (CN). MS (EI) *m/z* (relative intensity): m/z (%): 319 (6, M^+), 263 (24), 262 (100), 177 (67), 135 (57), 120 (82), 93 (46), 77 (74). Calcd for $C_{13}H_{18}N_2$: C 77.18; H 8.97; N 13.85. Found: C 76.86; H 8.95; N 13.83.

1-(1-Adamantan-1-yl-aziridin-2-yl)ethanone 5c.[8] White solid (180 mg, 82%), m.p. 48-49 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45-1.56 (m, 9H, Ad), 1.57-1.67 (m, 3H, Ad), 1.81 (dd, *J* = 2.7, 1.3 Hz, CH, CH_2), 1.96-2.00 (m, 1H, CH_2), 1.99 (s, 3H, CH_3), 2.00-2.07 (m, 3H, Ad), 2.41 (dd, *J* = 6.7, 2.7 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.8 (CH_3), 26.9 (CH_2), 29.5, 36.8, 40.3, 53.4 (Ad), 36.7 (CH), 209.4 (C=O); ^{15}N NMR ($CDCl_3$, 40 MHz): δ -320.2. IR (cm^{-1}): *v* 1700 (C=O). MS (EI) *m/z* (relative intensity): m/z (%): 219 (4, M^+), 178 (16), 135 (100), 93 (10), 79 (31), 67 (14), 41 (22). Calcd for $C_{14}H_{21}NO$: C 76.67; H 9.65; N 6.39. Found: C 76.31; H 9.56; N 6.24.

Methyl (1-adamantan-1-yl)-3-methylaziridine-2-carboxylate 5d. Colorless oil (167 mg, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (d, *J* = 5.5 Hz, 3H, $\underline{CH_3}CH$), 1.37-1.70 (m, 13H, Ad), 1.97-2.10 (m, 3H, Ad), 2.18-2.26 (m, 1H, $\underline{CH}CH_3$), 2.47 (d, *J* = 6.6 Hz, 1H, CHC=O), 3.68 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5 ($\underline{CH_3}C$), 29.4, 38.8, 40.1, 53.5 (Ad), 32.7 ($\underline{CH}CH_3$), 34.3 (CHC=O), 52.0 (CH_3O) 171.5 (C=O). IR (cm^{-1}): *v* 1748 (C=O). HRMS (ESI, m/z) calcd for $C_{15}H_{24}NO_2$ 250.1807; found 250.1806.

Adamantan-1-yl-(2-benzenesulfonyl-2-bromoethyl)amine 4: Yellow oil (324 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (br. s, 1H, NH); 1.50-1.69 (m, 12H, Ad); 2.03 (br.s, 3H, Ad); 3.10 (dd, *J* = 13.3, 8.4 Hz, 1H, CH_2); 3.50 (dd, *J* = 13.3, 4.4 Hz, 1H, CH_2); 4.80 (dd, *J* = 8.4, 4.4 Hz, 1H, CH); 7.54-7.58 (m, 2H, C_6H_5); 7.65-7.70 (m, 1H, C_6H_5); 7.92-7.95 (m, 2H, C_6H_5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 29.5, 36.5, 42.8, 50.9 (Ad); 42.4 (C-N); 66.7 (C-S); 129.1, 129.9, 134.6, 135.9 (C_6H_5). IR (cm^{-1}): *v* 1150, 1310 (SO_2); 3325 (N-H). MS, (EI) *m/z* (relative intensity): m/z (%): 399 (1, M^+ + 1); 297(1, M^+ - 1); 342 (18); 340 (18); 164 (100); 135 (95). Calcd. for $C_{18}H_{24}BrNO_2S$: C 54.27; H 6.07; N 3.52; S 8.05. Found: C 54.44; H 6.21; N 3.55; S 7.94.

Under high pressure: The mixture of 1-aminoadamantane (151 mg, 1 mmol), Michael acceptor (**3f-h**) (2 mmol), and triethylamine (111 mg, 1.1 mmol) in solvent (2 mL) was placed in a Teflon reaction vessel and pressurized to 10 kbar at room temperature for the corresponding time. After that, the pressure was released and the mixture was concentrated *in vacuo*. The crude product

was purified by column chromatography (Silica gel, pentane/ether, 9/1 (for **5d, 6a, 7**), 7/3 (for **5e, 6b**), The following compounds were prepared according to this procedure.

1-(1-Adamantan-1-yl)-3-phenylaziridin-2-yl)ethanone 5e: Colorless oil (115 mg, 39%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.50-1.70 (m, 12H, Ad), 1.56 (s, 3H, CH_3), 2.00-2.15 (m, 3H, Ad), 2.79 (d, J = 6.4 Hz, 1H, CHC(O)), 3.38 (d, J = 6.4 Hz, 1H, CHPh), 7.15-7.27 (m, 3H, Ph), 7.34-7.38 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3 (CH_3), 29.5, 36.8, 40.4, 53.4 (Ad), 40.6 (CHPh), 44.6 (CHC(O)), 127.4, 128.2, 128.3, 136.9 (Ph), 208.6 (C=O). IR (cm^{-1}): ν 1699 (C=O). HRMS (ESI, m/z) calcd for $C_{20}H_{26}NO$ 296.2014; found 296.2010.

Methyl 2-bromo-3-methoxybutanoate 6a: Dark brown oil (68 mg, 32%). (53:47) Mixture of two diastereomers. *Major isomer*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (d, J = 6.2 Hz, 3H, CH_3), 3.34 (s, 3H, CH_3O), 3.60-3.75 (m, 1H, CHBr), 3.77 (s, 3H, $CH_3OC(O)$), 4.32 (d, J = 6.5 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.4 (CH_3), 48.2 (CHBr), 53.0 (CH_3O), 57.4 ($CH_3C(O)$), 77.3 (CHO), 168.8 (C=O). *Minor isomer*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (d, J = 6.2 Hz, 3H, CH_3), 3.10 (s, 3H, CH_3O), 3.60-3.75 (m, 1H, CHBr), 3.77 (s, 3H, $CH_3OC(O)$), 4.18 (d, J = 8.3 Hz, 1H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.7 (CH_3), 49.9 (CHBr), 53.1 (CH_3O), 57.5 ($CH_3C(O)$), 77.5 (CHO), 169.5 (C=O). IR (cm^{-1}): ν 1743 (C=O). HRMS (ESI, m/z) calcd for $C_6H_{11}BrO_3$ 211.9892; found 211.9898.

3-Bromo-4-methoxy-4-phenylbutan-2-one 6b: Pale yellow oil (31 mg, 12%). (51:49) Mixture of two diastereomers. *Major isomer*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H, $CH_3C(O)$), 3.18 (s, 3H, CH_3O), 4.43 (d, J = 7.6 Hz, 1H, CH), 4.55 (d, J = 7.6 Hz, 1H, CHBr), 7.25-7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.6 ($CH_3C(O)$), 57.3 (CH_3O), 57.7 (CHBr), 84.1 (CHO), 128.1, 128.9, 129.1, 137.3 (Ph), 201.1 (C=O). *Minor isomer*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.15 (s, 3H, $CH_3C(O)$), 3.26 (s, 3H, CH_3O), 4.23 (d, J = 9.5 Hz, 1H, CH), 4.52 (d, J = 9.5 Hz, 1H, CHBr), 7.25-7.40 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.8 ($CH_3C(O)$), 54.4 (CH3O), 57.6 (CHBr), 82.7 (CHO), 127.9, 128.7, 129.1, 137.2 (Ph), 201.0 (C=O). IR (cm^{-1}): ν 1720 (C=O). HRMS (ESI, m/z) calcd for $C_{11}H_{14}BrO_2$ 258.0106; found 258.0106.

Ethyl (1-adamantan-1-ylamino)-3-methylbut-3-enoate 7: Colorless oil (105 mg, 38%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, J = 7.2 Hz, 3H, CH_3CH_2), 1.47-1.70 (m, 12H, Ad), 1.77 (s, 3H, CH_3), 1.81 (s, 1H, NH), 2.00-2.05 (m, 3H, Ad), 3.90 (s, 1H, CH), 4.17 (q, J = 7.2 Hz, 2H, CH_2), 4.84-4.87 (m, 1H, CH_2=), 4.93-4.96 (m, 1H, CH_2=); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.3 (CH_3CH_2), 20.0 (CH_3C), 29.8, 36.7, 43.1, 51.2 (Ad), 59.3 (CH), 61.1 (CH_2), 112.9 (CH_2=), 144.7

(=C), 175.2 (C=O). IR (cm^{-1}): *ν* 1736 (C=O), 3327 (NH). HRMS (ESI, m/z) calcd for $C_{17}H_{27}NO_2$ 278.2120; found 278.2114.

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