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A direct link between the Passerini reaction and α-lactams☆

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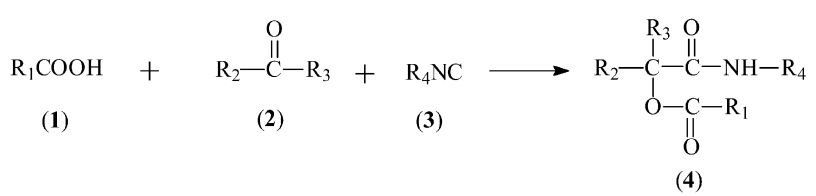
Abstract—α-Lactams (aziridinones) can function to replace two of the three reactants, the oxo-compound and the isonitrile, in the Passerini reaction. Four α-lactams (**5a-d**) were reacted with mono- and dicarboxylic acids of positive pK_a values to give 2-acyloxycarboxamides (**4**) and bis-2-acyloxycarboxamide products **12** and **13**, respectively. The same compounds were also prepared via the Passerini reaction. Acids with a negative pK_a decarbonylate α-lactams to give immonium salts. The main path of the reaction depends on the pK_a of the acid component, the reactivity of the α-lactam, and the reaction conditions.

1. Introduction

In 1921, Mario Passerini reported[2] that the one-pot, three-component reaction between a carboxylic acid (**1**), an aldehyde or ketone (**2**), and an isonitrile (**3**) yields α-acyloxycarboxamides (**4**) (Scheme 1). The yields of type **4** products reported by Passerini himself varied between 14[3] and 87%,[4] depending on the substituents in the reactants. Since then, this reaction, named the Passerini reaction, has been used widely, as documented in several extensive reviews[5–8].

About 40 years later, the synthesis of α-lactams (aziridinones) (**5**) has been achieved, and their reactions studied[9]. α-Lactams are the first stable representatives of three-membered ring carbonyl compounds to have been isolated in pure state. As summarized in a 1968 review[9] and in later published reports, ionic aprotic nucleophiles, such as *tert*-butoxide,[10] phenyl magnesium bromide,[11] or lithium aluminum hydride[12] effect ring-opening with cleavage of the lactam bond (the 1–2 bond), to give α-amino acid derivatives (**6**), while non-ionic protic nucleophiles, such as water, *tert*-butyl alcohol, benzylamine, glycine ethyl ester, α-toluenethiol, etc. cause ring-opening with cleavage of the 1–3 bond, to yield α-substituted carboxamides (**7**)[10] (Scheme 2). There are, however, a number of published reports,[13–16] which contradict the above general rule of ring-opening of stable α-lactams. The reactions of α-lactams with amines appear to be especially complicated, the products often being mixtures derived from competing modes of ring-opening. The factors governing regioselectivity in nucleophilic ring-opening of stable α-lactams have not been fully enumerated to date, although substantial progress has been made.[17,18] While unsubstituted aziridinone itself is still unknown, and appears to be unstable, the structural prerequisites that lend stability to this class of compounds are a tertiary alkyl substituent in position 1 and a tertiary alkyl or aryl substituent in position 3.

The predominant general path of thermal decomposition of most stable α-lactams prepared to date is fragmentation into an aldehyde or ketone (**2**) and an isonitrile (**3**), via the



Scheme 1. The Passerini reaction.

☆ See Ref. 1.

Keywords: Aziridinones; Maleic anhydride; Mono- and dicarboxylic acids; Nucleophilic substitution; Passerini reaction.
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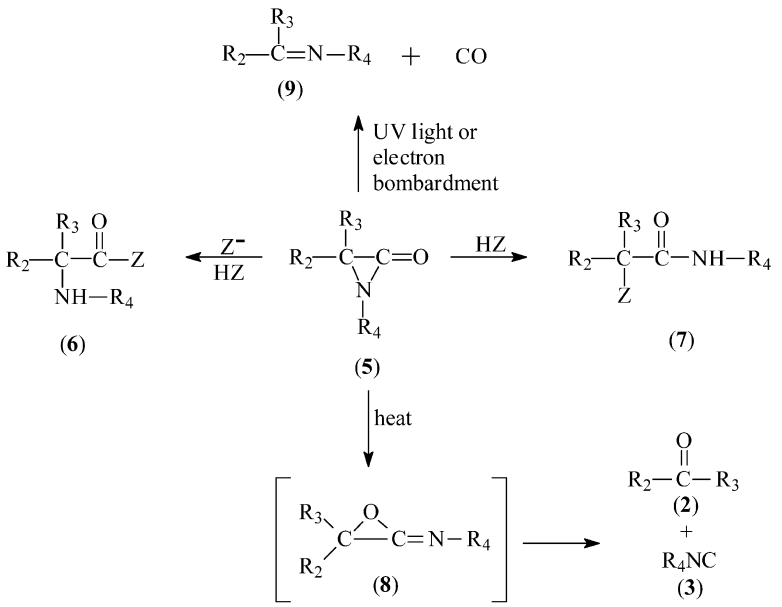


Scheme 2. Nucleophilic ring cleavage of α-lactams, and their thermal, photolytic, and electron bombardment induced decomposition.

imino-oxirane intermediate **8**[19] (Scheme 2). This thermal decomposition path of α-lactams is in sharp contrast with their electron impact-induced fragmentation,[20–22] ultraviolet photolysis,[23] and reaction with strong, non-aqueous mineral acids (e.g., HCl in ether[24]), all of which lead to Schiff bases (**9**) or their salts (**10**), and carbon monoxide (Scheme 2). An imino-oxirane intermediate (**8**) has also been postulated in the oxidation of ketenimines (**11**) with peracids,[25,26] which yields oxo-compounds (**2**) and isonitriles (**3**), along with minor amounts (~20%) of α-acyloxycarboxamides (**4**) (Scheme 3).

2. Results and discussion

2.1. Reaction of α-lactams with monocarboxylic acids

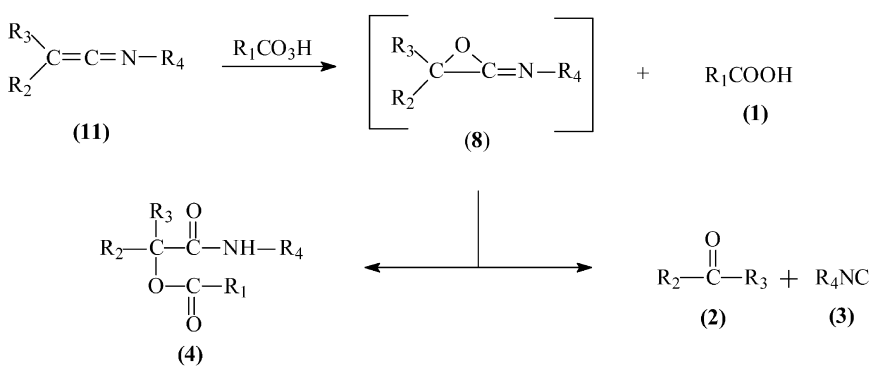
Heretofore, it went unnoticed that there is a connection between α-lactams and the Passerini reaction.[27]

For this study, we have chosen four α-lactams for their greatly varying thermal stability and reactivity, viz. 1-*tert*-butyl-3,3-dimethylaziridinone (**5a**),[10] 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**),[28] 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**),[20] and 1,3-di-*tert*-butylaziridinone (**5d**)[29] and five monocarboxylic acids, viz. acetic acid (**1a**), pivalic acid (**1b**), benzoic acid (**1c**), *trans*-cinnamic acid (**1d**), and trifluoroacetic acid (**1e**), as well as hydrofluoric acid.

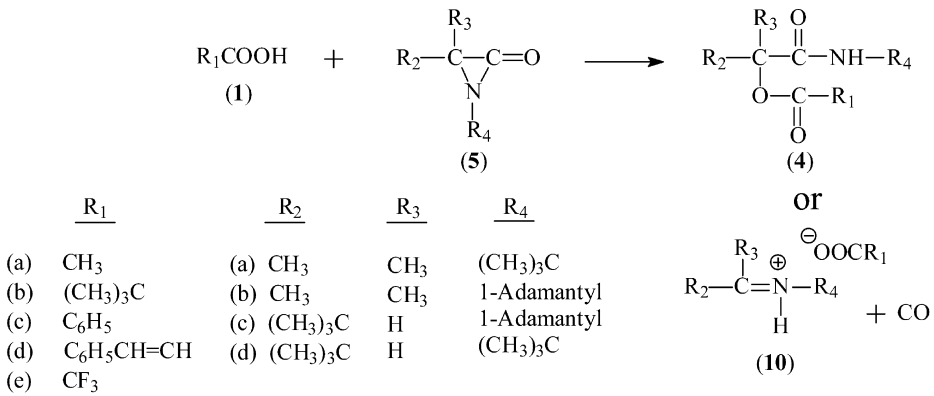
We have found that α-lactams readily react with carboxylic acids (**1**) to give α-acyloxycarboxamides (**4**) (Scheme 4), that is, α-lactams are capable of replacing two of the three reactants in the Passerini reaction (the aldehyde or ketone and the isonitrile), and the yields are comparable. An important advantage of this new synthesis of α-acyloxycarboxamides (**4**) is that it obviates the necessity of working with the repulsive-smelling isonitriles. Naturally, all the reactions have to be performed under sufficiently mild conditions to preclude the concurrent spontaneous decomposition of the α-lactam. The yields of products (**4**) from the reaction of α-lactams **5a**-**d** with monocarboxylic acids **1a**-**e** and from the Passerini reaction are listed in Table 1.

2.2. Reaction of α-lactams with dicarboxylic acids

The reaction described above can also be extended to dicarboxylic acids. Thus, α-lactams **5a** and **5b** with maleic



Scheme 3. The oxidation of ketenimines with peracids.



Scheme 4. The reaction of α-lactams with monocarboxylic acids.

acid, and α-lactams **5a-d** with succinic acid gave bis-Passerini products **12** and **13**, respectively. The same compounds can also readily be prepared by the Passerini reaction (Scheme 5).

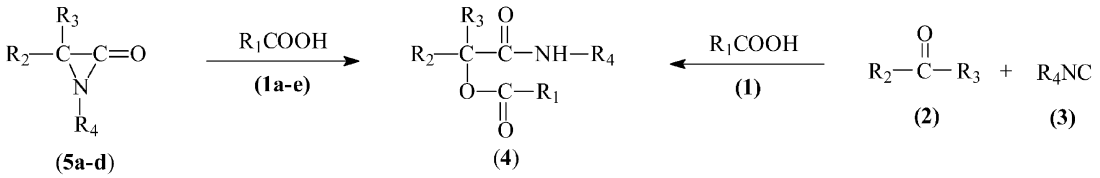
We reported earlier[30] that treatment of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**) with maleic acid in dioxane solution yields di-(*N*-1-adamantylneopentylidenimmonium) maleate (**14**), mp 191 °C (dec.), along with carbon monoxide, rather than a bis-Passerini product (Scheme 6). Whether the reaction of α-lactams with acids yields a Passerini product or an immonium salt depends on three factors: (1) the pK_a of the acid, (2) the relative reactivity of the α-lactam, (3) the reaction conditions. Of these, the first factor is the most determining one.

Ordinary saturated or unsaturated aliphatic and aromatic mono- and dicarboxylic acids react with α-lactams to give the Passerini product, while strong non-aqueous mineral acids, such as hydrochloric acid, hydrobromic acid, and *p*-toluenesulfonic acid cause decarbonylation with the formation of immonium salts (Scheme 7). If water is present, the immonium salts are hydrolyzed to an aldehyde or ketone and an amine.[24]

We concur with the observation of Bott,[24b] that even though ordinary amide-resonance is diminished in α-lactams because of the small-ring strain, it still contributes significantly to their stability. If *N*-protonation suppresses this amide-resonance, α-lactams decompose immediately and quantitatively, even at room temperature (Scheme 7).

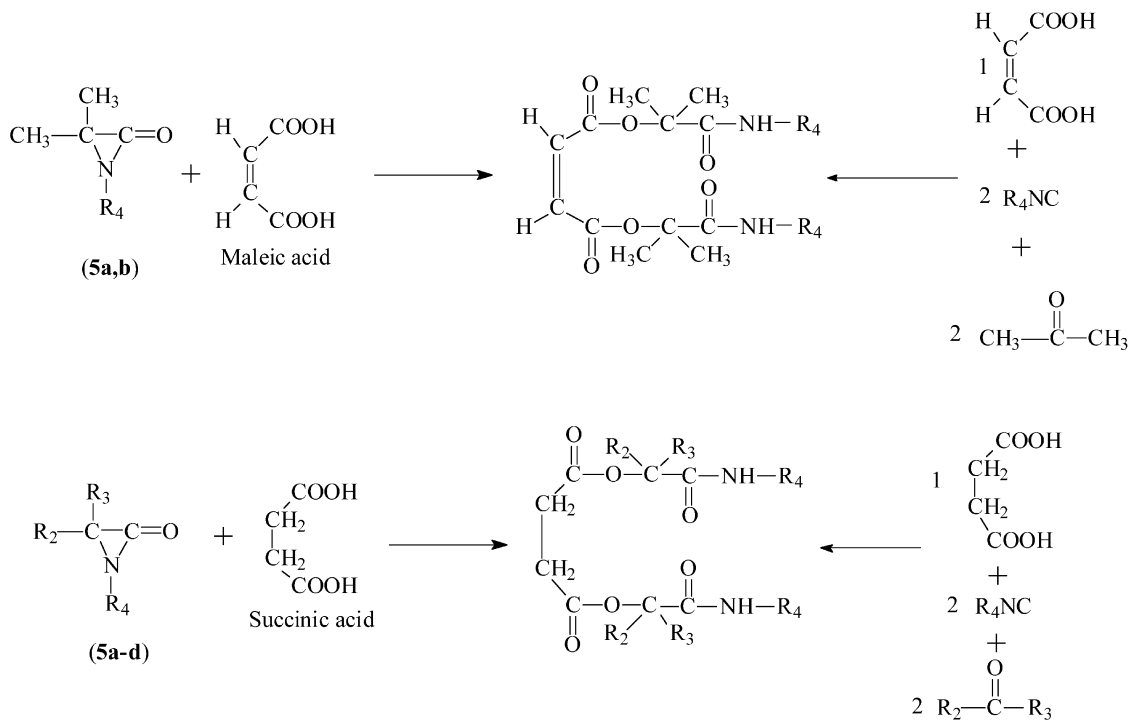
According to the evidence presented in this paper, the protonating power of carboxylic acids with a positive pK_a is

Table 1. The yields of products from the reaction of α-lactams

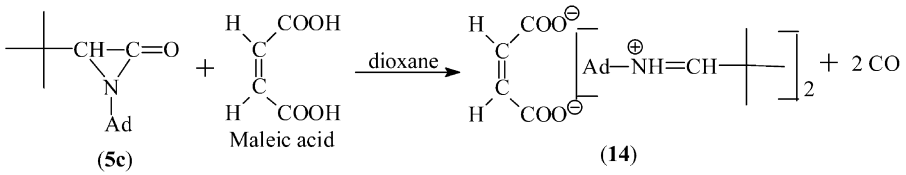


	R_1	R_2	R_3	R_4	Yield[a] (%)	Yield[b] (%)
4a	CH_3	CH_3	CH_3	t-C_4H_9	37	66
4b	t-C_4H_9	CH_3	CH_3	t-C_4H_9	66	45
4c	C_6H_5	CH_3	CH_3	t-C_4H_9	67	76
4d	$C_6H_5CH{=}CH$	CH_3	CH_3	t-C_4H_9	84	54
4e	CF_3	CH_3	CH_3	t-C_4H_9	66	47
4f	CH_3	CH_3	CH_3	1-Ad	81	50
4g	t-C_4H_9	CH_3	CH_3	1-Ad	74	29
4h	C_6H_5	CH_3	CH_3	1-Ad	75	32
4i	$C_6H_5CH{=}CH$	CH_3	CH_3	1-Ad	60	23
4j	CF_3	CH_3	CH_3	1-Ad	41	75
4k	CH_3	t-C_4H_9	H	1-Ad	63	57
4l	t-C_4H_9	t-C_4H_9	H	1-Ad	36	54
4m	C_6H_5	t-C_4H_9	H	1-Ad	58	68
4n	$C_6H_5CH{=}CH$	t-C_4H_9	H	1-Ad	74	75
4o	CF_3	t-C_4H_9	H	1-Ad	Decarbonylates	70
4p	CH_3	t-C_4H_9	H	t-C_4H_9	67	42
4q	t-C_4H_9	t-C_4H_9	H	t-C_4H_9	80	81
4r	C_6H_5	t-C_4H_9	H	t-C_4H_9	38	45
4s	$C_6H_5CH{=}CH$	t-C_4H_9	H	t-C_4H_9	65	33
4t	CF_3	t-C_4H_9	H	t-C_4H_9	Decarbonylates	72

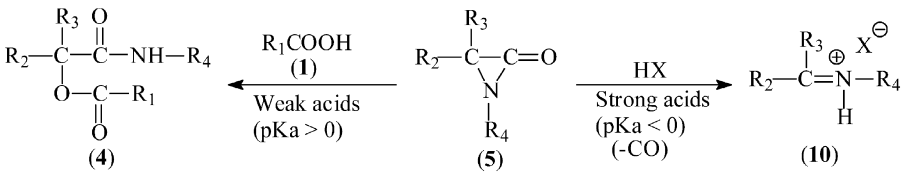
[a] Monocarboxylic acids.
[b] Passerini reaction.



Scheme 5. The reaction of α-lactams with dicarboxylic acids and the corresponding Passerini reactions.

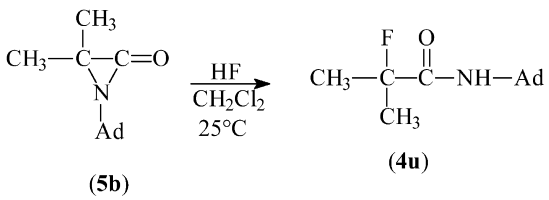


Scheme 6. Reaction of 1-(1-adamantyl)-3-*t*-butylaziridinone (**5c**) with maleic acid.



Scheme 7. Dependence of the product on the pK_a of the acid (see also Table 2).

insufficient to lead to decarbonylation, instead it leads to a Passerini product by nucleophilic substitution at C-3 (Scheme 7). Thus, while α-lactam **5b** reacts with hydrofluoric acid at room temperature to give 2-fluoro-2-methyl-*N*-(1-adamantyl)propanamide (**4u**) in good yield (Scheme 8), treatment of α-lactam **5c** with aqueous hydrobromic acid at room temperature leads to decarbonylation and a good yield of pivalaldehyde, isolated as the semicarbazone, and a nearly quantitative yield of 1-adamantanamine (Scheme 9).

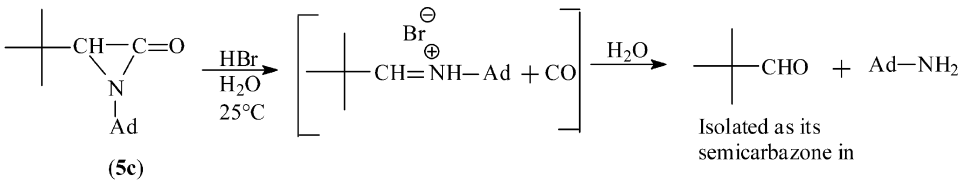


Scheme 8. Reaction of α-lactam **5b** with hydrofluoric acid.

It appears that the acid-strength where the turning point in the reaction path occurs is around a pK_a of zero. So, the acids in the left column of Table 2 will give a Passerini product with α-lactams, while those in the right-side column will

Table 2. The pK_a values of selected acids[31]

'Weak acid'	pK_a	'Strong acid'	pK_a
Pivalic acid	5.03	Benzenesulfonic acid	−0.6
Acetic acid	4.8	Methanesulfonic acid	−1.2
trans-Cinnamic acid	4.44	Sulfuric acid	−5.0
Benzoic acid	4.2	*p*-Toluenesulfonic acid	−6.6
Succinic acid	4.16, 5.61	Hydrochloric acid	−7
Formic acid	3.8	Hydrobromic acid	−9
Phthalic acid	3.51, 4.82	Hydroiodic acid	−10
Hydrofluoric acid	3.2		
Maleic acid	1.83, 6.07		
Trifluoroacetic acid	0.2		



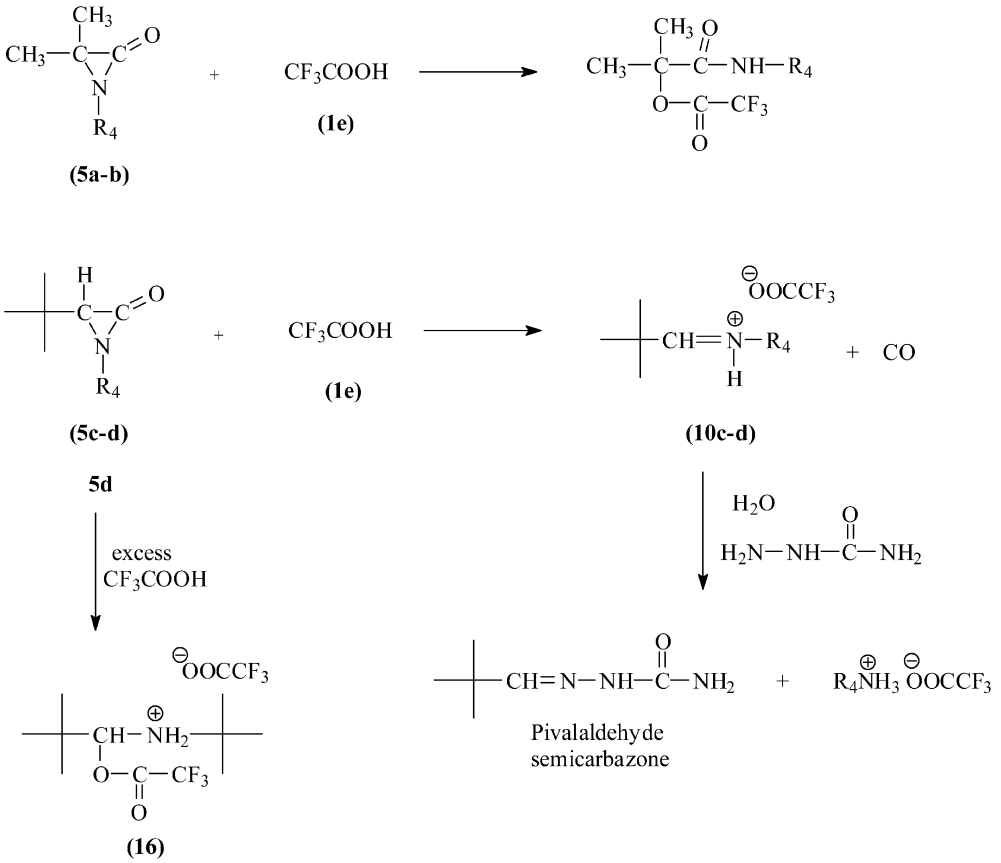
Scheme 9. Reaction of α-lactam **5c** with hydrobromic acid.

cause decarbonylation as the predominant reaction path. Trifluoroacetic acid (**1e**), the pK_a of which is at or near the turning point, gives both, depending on the relative reactivity of the α-lactam. Thus, the two more reactive α-lactams (**5a**, **5b**) give Passerini products (**4e**, **4j**), while the two less reactive ones (**5c**, **5d**) decarbonylate upon treatment with trifluoroacetic acid to immonium trifluoroacetates **10c-d**. After work-up, 1-adamantan ammonium trifluoroacetate (**15c**) was isolated from **5c** and *tert*-butyl ammonium trifluoroacetate (**15d**) or *N*-*tert*-butyl-2,2-dimethyl-1-(trifluoroacetyl)oxypropan-1-aminium trifluoroacetate (**16**) was isolated from **5d**, in excellent yield.

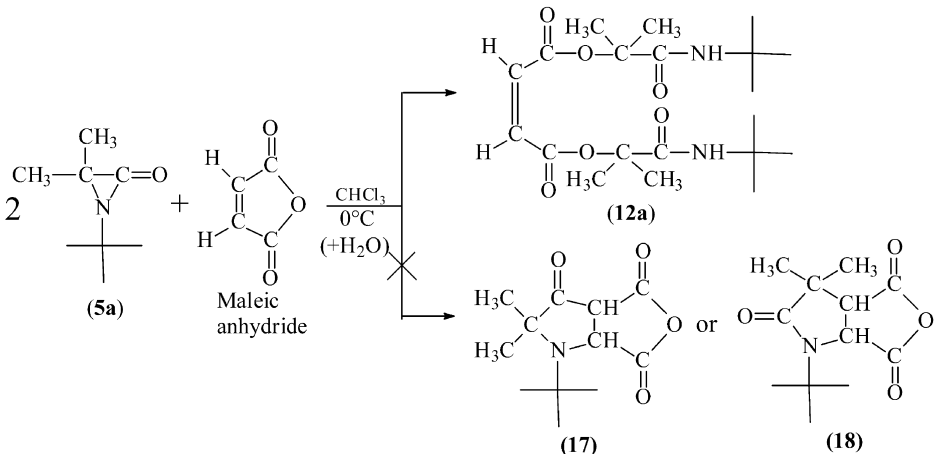
In separate experiments, both hydrolysis products, pivalaldehyde and 1-adamantanamine, were isolated from **5c**, the former as its semicarbazone. Pivalaldehyde semicarbazone was also isolated from the reaction of **5d** with CF_3COOH and subsequent hydrolysis of the intermediate salt **10d** (Scheme 10). Because of the low boiling point of *tert*-butylamine (bp 44–46 °C), it was removed with the solvent upon evaporation.

2.3. Reaction of α-lactams with maleic anhydride

It has been reported[32] that maleic anhydride is an excellent 'dipolarophile' in 1,3-dipolar cycloaddition reactions. We found indeed that α-lactam **5a** undergoes smooth and rapid reaction with maleic anhydride, even at 0 °C in $CHCl_3$. However, the product isolated after chromatography on alumina is not a 3+2=5 type cycloadduct (**17** or **18**), but the bis-Passerini product di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (**12a**), representing a 2:1 addition without decarbonylation, even if the two reactants are applied in an equimolar ratio (Scheme 11). It should be noted that this product is obtained even when freshly vacuum-sublimed maleic anhydride is used. This same product was also readily obtained from α-lactam **5a** and maleic acid, and by the Passerini reaction from maleic acid, acetone, and *tert*-butyl isonitrile (Scheme 5), cf. Section 4. This result is the more surprising since α-lactam **5a** has been reported to undergo successful 1,3-dipolar cycloaddition reaction with three different 'dipolarophiles', viz. phenylisocyanate,[33] diphenylketene,[34] and *N*,*N*-dimethylformamide.[35]



Scheme 10. Reactions of α-lactams **5a-d** with trifluoroacetic acid.



Scheme 11. The reaction of α-lactam **5a** with maleic anhydride.

We include these results here because they represent a striking example of an α-lactam leading to a bis-Passerini product, even though no mechanistic investigation was undertaken to date to fully account for the reaction. It is evident, however, that the absence of a strong acid preserves the α-lactam ring from decarbonylation so that it can undergo nucleophilic ring-opening. Under comparable conditions (0–25 °C, in $CHCl_3$ or CCl_4 solution), α-lactams **5b-d** do not react with maleic anhydride. When a 2:1 mixture of α-lactam **5b** and maleic anhydride is heated to 70 °C for 10 min in carbon tetrachloride solution, the characteristic α-lactam carbonyl band in the IR at ~1840 cm^{-1} completely disappears. However, under these forced conditions, several parallel reactions occur simultaneously and concurrently:

(a) Passerini reaction, leading to a low yield (17%) of the bis-Passerini product (**12b**),
(b) spontaneous thermal decomposition of the α-lactam, leading to acetone (not isolated) and 1-adamantyl isonitrile (26%),
(c) formation of a bright purple dye (~51%) which stays at the top of the silica gel column during chromatography and was not investigated further.

As we reported earlier,[30] α-lactam **5c** also reacts with maleic anhydride, but only at 80 °C, and under the more severe conditions required for this reaction, decarbonylation occurs and the products are *N*-(1-adamantyl) maleamic acid (**19**), pivalaldehyde (**20**), and carbon monoxide (Scheme 12). The details of this complicated reaction have been studied, and a four-step mechanism, based on acid-catalyzed decarbonylation and hydrolysis, has been proposed.[30] Control experiments on **5a-d** with benzoic and succinic anhydride under comparable conditions (0–25 °C, in $CHCl_3$ or CCl_4 solution) led to no detectable reaction.

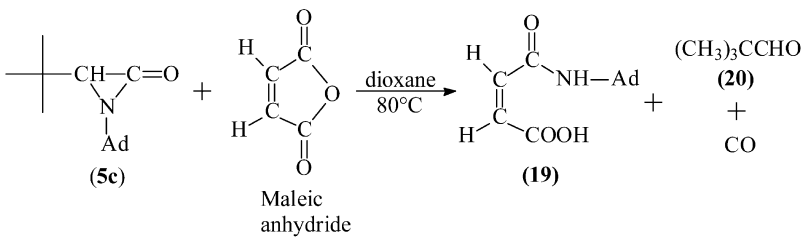
3. Conclusions

α-Lactams **5a-d** react with ordinary aliphatic and aromatic mono- and dicarboxylic acids and hydrofluoric acid to give Passerini products **4** and **12-13**, whereas reaction with stronger acids leads to immonium salts, for example, **10** with concomitant decarbonylation, in agreement with an earlier report.[24] The major path of the reaction depends on a combination of three factors:

(1) the pK_a of the acid: a positive pK_a favors Passerini product formation, while a negative pK_a leads to decarbonylation.
(2) the relative reactivity of the α-lactam: higher reactivity favors Passerini product.
(3) the reaction conditions: milder reaction conditions favor Passerini product.

An advantage of this synthesis of α-acyloxycarboxamides from α-lactams is that it obviates the necessity of working with the repulsive-smelling isonitriles.

α-Lactams **5a** and **5b** also react with maleic anhydride to give the bis-Passerini product **12a** and **12b**, respectively, rather than a cycloadduct (**17** or **18**).



Scheme 12. The reaction of α-lactam **5c** with maleic anhydride.

4. Experimental

Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz Bruker instrument with tetramethylsilane as internal standard. Chemical shifts are reported in ppm (δ). IR spectra were measured on a Perkin–Elmer Spectrum 1000 FT-IR. Microanalyses were preformed by Atlantic Microlab Inc., Norcross, GA. Mass spectra (MS) were recorded on a Hewlett–Packard GC–MS GCD system. For column chromatography, JT Baker Silica gel (40 μm) was used. Thin layer chromatography (TLC) was preformed with Analtech silica gel glass backed plates (250 μm). The aziridinones were prepared by the method of Scrimin et al.[36] except where noted otherwise.

4.1. Reactions of α-lactams with carboxylic acids

4.1.1. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with acetic acid. *N*-*tert*-Butyl-2-acetoxy-2-methylpropanamide (4a). The toluene solution of the α-lactam 1-*tert*-butyl-3,3-dimethylaziridinone[10] (**5a**) (0.565 g, 0.004 mol) was cooled to 0 °C and 2 equiv. of acetic acid (0.48 g, 0.008 mol) dissolved in toluene (2 mL) was added dropwise. After stirring for 1 h, the reaction mixture was washed with 5% sodium bicarbonate and twice with water (20 mL). The organic layer was dried with sodium sulfate and the solvent removed under reduced pressure to afford crude product **4a** (0.430 g, 53.4%). After recrystallization from 3 mL of *n*-heptane, a white solid **4a** (0.30 g, 37%) with mp 78–79 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.45. IR (CCl_4) ν: 3430, 2955, 1739, 1680, and 1505 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.55 (s, 6H), 2.02 (s, 3H), and 5.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 22.1, 24.4, 51.1, 81.8, 169.2, 172.2. MS: *m*/*z* 201, 186, 158, 144, 129, 115, 102, 101, 88, 86, 61, 59, 58, 57, 43 (base peak).

4.1.2. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with pivalic acid. *N*-*tert*-Butyl-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4b). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.318 g, 2.25 mmol) in 25 mL of toluene at 0 °C was added 0.689 g (6.75 mmol) of pivalic acid in 10 mL of anhydrous toluene. The solution was stirred overnight slowly coming to rt for 20 h then was washed with 4×35 mL of 5% $NaHCO_3$ and 2×35 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.46 g of a white solid. After flash chromatography (95% *n*-hexane/5% ethyl acetate), 0.36 g (66%) of a solid (**4b**) with mp 49–50 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3446, 2973, 2935, 1739, 1687 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.35 (s, 9H), 1.59 (s, 6H), 5.86 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.1, 28.6, 39.1, 50.8, 81.6, 172.4, 176.3. MS: *m*/*z* 243, 228, 186, 185, 171, 158, 144, 114, 103, 102, 86, 85, 59, 58, 57 (base peak), 41. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.28; H, 10.47; N, 5.78.

4.1.3. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with benzoic acid. *N*-*tert*-Butyl-2-benzoyloxy-2-methylpropanamide (4c). The toluene solution of the α-lactam 1-*tert*-butyl-3,3-dimethylaziridinone (**5a**) (0.565 g, 0.004 mol) was cooled to 0 °C and 2 equiv. of benzoic acid (0.98 g, 0.008 mol) dissolved in toluene (2 mL) was added dropwise. After stirring for 1 h, the reaction mixture was washed with 5% sodium bicarbonate and twice with water (20 mL). The organic layer was dried with sodium sulfate and the solvent removed under reduced pressure to afford crude product **4c** (0.81 g, 77.0%) with mp 88–89 °C. After recrystallization from *n*-heptane (1.5 mL), 0.70 g (66.5%) of a white solid with mp 89–90 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3435, 3050, 2955, 1722, 1680, 1505 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.72 (s, 6H), 5.89 (s, 1H), and 7.44 (t, 2H, *J*=7.7 Hz), 7.56 (t, 1H, *J*=7.5 Hz), 7.97 (d, 2H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 24.7, 28.8, 51.2, 82.5, 128.7, 129.6, 130.7, 133.4, 164.9, and 172.3. MS: *m*/*z* 263, 205, 191, 164, 146, 123, 105 (base peak), 77, 59, 57. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.26; H, 8.00; N, 5.22.

4.1.4. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with *trans*-cinnamic acid. *N*-*tert*-Butyl-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4d). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.318 g, 2.25 mmol) in 25 mL of toluene at 0 °C was added 1.00 g (6.75 mmol) of *trans*-cinnamic acid in 10 mL of anhydrous toluene. The solution was stirred overnight slowly coming to rt for 18.5 h then was washed with 4×35 mL of 5% $NaHCO_3$ and 2×35 mL of distilled water, dried with Na_2SO_4, filtered and rotary-evaporated to give 0.60 g of a yellow solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.55 g (84%) of a white solid (**4d**) with mp 102–104 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.50. IR (CCl_4) ν: 3447, 3030, 2975, 1722, 1688, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H), 1.68 (s, 6H), 5.87 (s, 1H, exchangeable in D_2O), 6.43 (d, 1H, *J*=16.0 Hz), 7.41 (q, 3H, *J*=2.6 Hz), 7.54 (quintuplet, 2H, *J*=2.6 Hz), 7.68 (d, 1H, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.6, 51.0, 81.9, 118.3, 128.1, 129.0, 130.5, 134.2, 145.4, 165.1, 172.2. MS: *m*/*z* 231, 217, 190, 175, 172, 145, 131 (base peak), 103, 77, 59, 57, 51, 41. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.32; H, 7.94; N, 4.83.

4.1.5. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with trifluoroacetic acid. *N*-*tert*-Butyl-2-methyl-2-trifluoroacetoxypropanamide (4e). 1-*tert*-Butyl-3,3-dimethylaziridinone (**5a**) (0.565 g, 0.004 mol) was dissolved in toluene (30 mL). A solution of trifluoroacetic acid (0.92 g, 0.008 mol) in toluene (2 mL) was added dropwise at 0 °C. After stirring for 1 h, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the toluene was removed under reduced pressure to afford 0.47 g (83%) of an oil which partially solidified after 2 days. 0.37 g (65.5%) of pure **4e** was obtained by sublimation (40–50 °C, 11 mm), mp 46–47 °C. TLC (90% *n*-hexane/10% isopropyl alcohol) R_f=0.45. IR (CCl_4) ν: 3454, 2970, 1793, 1690 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.70 (s, 6H), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.7, 28.5, 51.5, 87.0, 114.3 (q, *J*=286.5 Hz), 155.0 (q, *J*=42.0 Hz), 169.9. MS: *m*/*z* 255, 240, 184, 155, 126, 114, 98, 86, 69, 57 (base peak), 41. Anal. Calcd for $C_{10}H_{16}NO_3F_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 47.32; H, 6.51; N, 5.57.

4.1.6. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with acetic acid. *N*-(1-Adamantyl)-2-acetoxy-2-methylpropanamide (4f). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone[28] (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 0.502 g (8.35 mmol) of acetic acid. The solution was stirred for 2.5 h then was washed with 3×10 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.51 g of a white solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.38 g (81%) of a white solid (**4f**) with mp 157–158 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.20. IR (CCl_4) ν: 3439, 2910, 2848, 1750, 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.59 (s, 6H), 1.69 (s, 6H), 2.00 (s, 6H), 2.07 (s, 6H), 5.67 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 22.0, 24.3, 29.5, 36.4, 41.4, 51.6, 81.7, 169.1, 171.9. MS: *m/z* 279, 236, 222, 219, 178, 176, 150, 135 (base peak), 102, 93, 79, 59, 43, 41. Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.05; H, 9.16; N, 4.91.

4.1.7. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with pivalic acid. *N*-(1-Adamantyl)-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4g). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 0.853 g (8.35 mmol) of pivalic acid. The solution was stirred for 4 h then was washed with 4×40 mL of 5% $NaHCO_3$ and 2×40 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.88 g of an oil. After flash chromatography (92.5% *n*-hexane/7.5% ethyl acetate), 0.40 g (74%) of a white solid (**4g**) with mp 65–67 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.41. IR (CCl_4) ν: 3438, 2910, 2852, 1739, 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.59 (s, 6H), 1.69 (s, 6H), 1.99 (s, 6H), 2.08 (s, 3H), 5.75 (bs, 1H, exchangeable in D_2O). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.2, 29.5, 36.4, 39.1, 41.5, 51.4, 81.6, 172.2, 176.3. MS: *m/z* 321, 306, 263, 236, 219, 220, 192, 163, 150, 144, 135 (base peak), 107, 103, 93, 85, 79, 67, 59, 57, 41. Anal. Calcd for $C_{19}H_{31}NO_3$: C, 70.99; H, 9.72; N, 4.36. Found: C, 71.01; H, 9.94; N, 4.29.

4.1.8. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with benzoic acid. *N*-(1-Adamantyl)-2-benzoyloxy-2-methylpropanamide (4h). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 1.02 g (8.35 mmol) of benzoic acid in 10 mL of benzene. The solution was stirred for 3 h then was washed with 4×40 mL of 5% $NaHCO_3$ and 2×40 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.54 g of a white solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.43 g (75%) of a white solid (**4h**) with mp 105–106 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.24. IR (CCl_4) ν: 3441, 2910, 2852, 1730, 1686 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.68 (s, 6H), 1.73 (s, 6H), 2.02 (s, 6H), 2.08 (s, 3H), 5.78 (bs, 1H, exchangeable in D_2O), 7.47 (t, 2H, *J*=7.0, 8.0 Hz), 7.59 (t, 1H, *J*=7.0 Hz), 8.00 (d, 2H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 24.6, 29.5, 36.4, 41.5, 51.7, 82.3, 128.5, 129.5, 130.7, 133.2, 164.8, 171.9. MS: *m/z* 341, 283, 240, 219, 193, 192, 191, 164, 135 (base peak), 105, 77, 59. Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 74.02; H, 8.03; N, 4.04.

4.1.9. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with *trans*-cinnamic acid. *N*-(1-Adamantyl)-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4i). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.493 g, 1.67 mmol) in 25 mL of benzene at rt was added 1.24 g (8.35 mmol) of *trans*-cinnamic acid in 10 mL of benzene. The solution was stirred for 5 h then was washed with 4×40 mL of 5% $NaHCO_3$ and 2×40 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.60 g of a light yellow solid. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.37 g (60%) of a white solid (**4i**) with mp 125–126 °C was obtained. TLC (85% *n*-hexane/15% ethyl acetate) R_f=0.39. IR (CCl_4) ν: 3438, 3064, 3029, 2910, 2851, 1722, 1686, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.68 (s, 12H), 2.03 (s, 6H), 2.08 (s, 3H), 5.74 (bs, 1H, exchangeable in D_2O), 6.42 (d, 1H, *J*=16.0 Hz), 7.40 (s, 3H), 7.53 (s, 2H), 7.68 (d, 1H, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$): δ 25.0, 29.8, 36.7, 41.8, 52.0, 82.2, 118.7, 128.5, 129.3, 130.9, 134.6, 145.7, 165.5, 172.3. MS: *m/z* 367, 309, 238, 219, 190, 175, 150, 145, 135 (base peak), 131, 107, 103, 93, 91, 79, 77, 59, 41. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.21; H, 8.13; N, 3.71.

4.1.10. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with trifluoroacetic acid. *N*-(1-Adamantyl)-2-methyl-2-trifluoroacetoxypropanamide (4j). To a solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**) (0.89 g, 0.004 mol) in 10 mL of ether at 0 °C, trifluoroacetic acid (0.570 g, 0.005 mol) was added. The solution was stirred for 3 h. The ether was removed under reduced pressure to afford crude *N*-(1-adamantyl)-2-methyl-2-trifluoroacetoxypropanamide **4j** (81.9%). After flash chromatography (70% *n*-hexane/30% ethyl acetate), 0.54 g (40.6%) of a white solid with mp 100–102 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.42. IR (CCl_4) ν: 3445, 2920, 2860, 1795, 1693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (t, *J*=2.7 Hz, 6H), 1.70 (s, 6H), 1.97 (d, *J*=2.7 Hz, 6H), 2.08 (s, 3H), 5.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 29.6, 36.4, 41.5, 52.2, 87.0, 114.4 (q, *J*=287.0 Hz), 155.4 (q, *J*=42.4 Hz), 169.7. MS: *m/z* 333, 219, 192, 176, 155, 135 (base peak), 107, 93, 69, 41. Anal. Calcd for $C_{16}H_{22}NF_3O_3$: C, 57.65; H, 6.65; N, 4.20. Found: C, 57.79; H, 6.67; N, 4.02.

4.1.11. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with acetic acid. *N*-(1-Adamantyl)-2-acetoxy-3,3-dimethylbutanamide (4k). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**)[20] (0.990 g, 0.004 mol) was dissolved in benzene (30 mL). Acetic acid (0.480 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% Na_2CO_3 (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4k** (88%). After flash chromatography (90% *n*-hexane/10% ethyl acetate), pure *N*-(1-adamantyl)-2-acetoxy-3,3-dimethylbutanamide was obtained (63%), mp 138–140 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.33. IR (CCl_4) ν: 3435, 3092, 3037, 2910, 2852, 1752, 1691 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.01 (s, 9H), 1.67 (s, 6H), 1.99 (s, 6H), 2.07 (s, 3H), 2.14 (s, 3H), 4.56 (s, 1H), 5.45 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 26.7, 29.8, 32.0, 34.4, 36.7, 42.0, 52.3, 81.5, 167.6, 170.1. MS: *m/z* 307, 251, 232, 207, 178, 150, 135 (base peak), 120, 93, 79, 57, 43. Anal. Calcd for

$C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.10; H, 9.53; N, 4.66.

4.1.12. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with pivalic acid. *N*-(1-Adamantyl)-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4l). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**) (0.75 g, 0.003 mol) was dissolved in benzene (30 mL). Pivalic acid was added (0.61 g, 0.006 mol) and the reaction was refluxed for 2 h. The reaction mixture was then washed with 5% $NaHCO_3$ (30 mL), and twice with H_2O (20 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure, to give a crude oil which solidified (0.95 g, 90.5%). Crude 4 l was flash chromatographed (90% *n*-hexane/10% ethyl acetate) to obtain pure *N*-(1-adamantyl)-2-(2,2-dimethylpropanoyloxy)-3,3-dimethylbutanamide (0.38 g, 36.2%), mp 90–92 °C. TLC (80% *n*-hexane/20% ethyl acetate): R_f=0.64. IR (CCl_4) ν: 3437, 2910, 1742, 1687 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.26 (s, 9H), 1.67 (s, 6H), 1.98 (s, 6H), 2.07 (s, 3H), 4.68 (s, 1H), 5.48 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 27.2, 29.4, 34.2, 36.3, 38.9, 41.6, 51.8, 80.6, 167.6, 176.5. MS: *m/z* 349, 293, 249, 232, 208, 172, 163, 135 (base peak), 117, 85, 70, 57. Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.26; H, 10.15; N, 4.05.

4.1.13. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with benzoic acid. *N*-(1-Adamantyl)-2-benzoyloxy-3,3-dimethylbutanamide (4m). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**) (0.75 g, 0.003 mol) was dissolved in benzene (30 mL). Benzoic acid (0.73 g, 0.006 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4m** (0.86 g, 77.5%). After flash chromatography (95% *n*-hexane/5% ethyl acetate), pure **4m** (0.645 g, 58.2%) was obtained, mp 163–165 °C. TLC (80% *n*-hexane/20% ethyl acetate): R_f=0.67. IR (CCl_4) ν: 3436, 2911, 2852, 1734, 1688, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.14 (s, 9H), 1.66 (s, 6H), 1.99 (s, 6H), 2.06 (s, 3H), 4.93 (s, 1H), 5.55 (s, 1H), 7.48 (m, 2H), 7.63 (m, 1H), 8.10 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.4, 34.4, 36.3, 41.6, 52.0, 81.5, 128.7, 133.4, 165.2, 167.2. MS: *m/z* 369, 313, 283, 269, 240, 208, 192, 177, 135 (base peak), 105, 79, 77, 70. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.79; H, 8.62; N, 3.69.

4.1.14. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with *trans*-cinnamic acid. *N*-(1-Adamantyl)-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4n). 1-(1-Adamantyl)-3-*tert*-butylaziridinone (**5c**) (0.75 g, 0.003 mol) was dissolved in benzene (30 mL). *trans*-Cinnamic acid (0.89 g, 0.006 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4n** (1.04 g, 100%). After recrystallization from 6 mL hot *n*-heptane, a white solid (0.77 g, 74.0%) with mp 122–123 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3429, 3060, 2910, 1732, 1687, 1638, 1549, 1512 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.67 (s, 6H), 2.00 (s, 6H), 2.07 (s, 3H), 4.82 (s, 1H), 5.54 (bs, 1H), 6.50 (d, J=16.0 Hz, 1H), 7.44 (m, 3H), 7.55 (dd, J=3.7 Hz, 2H), 7.76 (d, J=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 29.4, 34.2, 36.3, 41.6, 52.0, 81.1, 117.2, 128.3, 129.1, 130.7, 134.1, 146.0, 165.7, 167.3. MS (ES): *m/z* 417.9 (M+23), 395.8, 380.9, 313.1, 245.0. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.95; H, 8.39; N, 3.33.

4.1.15. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with acetic acid. *N*-*tert*-Butyl-2-acetoxy-3,3-dimethylbutanamide (4p). 1,3-di-*tert*-Butylaziridinone[29] (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). Acetic acid (0.48 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4p** (0.90 g, 98.1%) as an oil which solidified overnight. After recrystallization from 1 mL of *n*-hexane, 0.61 g (66.5%) of a white solid was obtained, mp 62–63 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.44. IR (CCl_4) ν: 3440, 2965, 1738, 1683, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (s, 9H), 2.11 (s, 3H), 4.64 (s, 1H), 5.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 26.4, 28.8, 34.2, 51.4, 81.2, 167.7, 169.9. MS: *m/z* 229, 214, 186, 173, 157, 131, 129, 87, 75, 57 (base peak), 43.

4.1.16. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with pivalic acid. *N*-*tert*-Butyl-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4q). 1,3-di-*tert*-Butylaziridinone (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). Pivalic acid (0.817 g, 0.008 mol) was added and the reaction refluxed for 30 min. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4q** (0.91 g, 83.8%). Crude **4q** was flash chromatographed (95% *n*-hexane/5% ethyl acetate) to obtain pure *N*-*tert*-butyl-2-(2,2-dimethylpropanoyloxy)-3,3-dimethylbutanamide (**4q**) (0.869 g, 80%), mp 87–88 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.48. IR (CCl_4) ν: 3427, 3370, 2955, 2860, 1735, 1667, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.99 (s, 9H), 1.24 (s, 9H), 1.30 (s, 9H), 4.66 (s, 1H), and 5.59 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.5, 27.3, 28.8, 34.4, 39.0, 51.3, 80.8, 167.8, and 176.7. MS: *m/z* 271, 256, 215, 199, 172, 157, 143, 130, 102, 85, 71, 57 (base peak), 41.

4.1.17. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with benzoic acid. *N*-*tert*-Butyl-2-benzoyloxy-3,3-dimethylbutanamide (4r). 1,3-di-*tert*-Butylaziridinone (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). Benzoic acid (0.98 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4r** (0.92 g, 79%). After recrystallization from *n*-heptane/ethyl acetate (5 mL/2 mL), 0.44 g (37.6%) of a white solid with mp 128–129 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.68. IR (CCl_4) ν: 3440, 3380, 3060, 2965, 2870, 1720, 1685, 1598, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.32 (s, 9H), 4.91 (s, 1H), 5.70 (s,

1H), 7.47 (m, 2H), 7.59 (m, 1H), 8.09 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.6, 51.4, 81.7, 128.8, 129.8, 133.6, 165.4, 167.6. MS: *m/z* 291, 276, 253, 235, 219, 192, 177, 143, 130, 105 (base peak), 87, 77, 70, 57, 41.

4.1.18. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with *trans*-cinnamic acid. *N*-*tert*-Butyl-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4s). 1,3-di-*tert*-Butylaziridinone (**5d**) (0.68 g, 0.004 mol) was dissolved in benzene (30 mL). *trans*-Cinnamic acid (1.19 g, 0.008 mol) was added and the reaction refluxed for 2 h. After cooling to rt, the reaction mixture was washed with 5% $NaHCO_3$ (30 mL) and twice with distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude **4s** (1.22 g, 96.2%). After recrystallization from methylene chloride/*n*-heptane (1 mL:3 mL), 0.83 g (65.4%) of a white solid was obtained, mp 97–98 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.46. IR (CCl_4) ν: 3440, 2960, 2868, 1715, 1680, 1633, 1505 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.33 (s, 9H), 4.81 (s, 1H), 5.70 (s, 1H), 6.50 (d, 1H, *J*=16.0 Hz), 7.38 (m, 3H), 7.54 (m, 2H), 7.74 (d, 1H, *J*=16.0 Hz). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.4, 51.4, 81.2, 117.3, 128.4, 129.1, 130.8, 134.2, 146.2, 165.8, 167.7. MS: *m/z* 317, 261, 245, 231, 218, 175, 162, 149, 131 (base peak), 103, 77, 70, 57, 41.

4.1.19. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with 1 equiv. of trifluoroacetic acid. 1-Adamantan ammonium trifluoroacetate (15c). Dropwise, over a period of 5 min, a solution of trifluoroacetic acid (0.659 g, 5.78 mmol) in 5 mL of THF was added to a solution of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**) (1.43 g, 5.78 mmol) in 20 mL of THF at 0 °C. The solution stirred for 3 h slowly reaching a temperature of 10 °C and then the THF was removed under reduced pressure to give 1.77 g of a white solid. It was recrystallized from hot *n*-heptane/isopropyl alcohol (15 mL:5 mL) to give 1.26 g (82%) of 1-adamantan ammonium trifluoroacetate (**15c**), mp 298–300 °C. IR (KBr) ν: 2914, 1668, 1541, 1455, 1365 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.59 (dd, 6H, *J*=10.0 Hz), 1.77 (s, 6H), 2.06 (s, 3H), 8.03 (bs, 3H, exchanges in D_2O). ^{13}C NMR (DMSO-d_6) δ 28.4, 35.2, 50.9, 117.1 (q, *J*=299.0 Hz), 158.6 (q, *J*=31.0 Hz). Anal. Calcd for $C_{12}H_{18}F_3NO_2$: C, 54.33; H, 6.84; N, 5.28. Found: C, 54.35; H, 6.76; N, 5.27.

4.1.20. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with trifluoroacetic acid followed by hydrolysis. To 0.36 g (1.46 mmol) of 1-(1-adamantyl)-3-*tert*-butylaziridinone in 10 mL of benzene was added a solution of trifluoroacetic acid (0.347 g, 3.04 mmol) in 5 mL of benzene and it stirred at rt for 66 h (immediately upon addition of trifluoroacetic acid gas evolution was observed). The benzene was removed under reduced pressure to yield a solid to which 9 mL of hexane was added and the mixture was stored at −20 °C for several hours. It was then filtered to give 0.481 g of a white solid, which was added to a solution of semicarbazide hydrochloride (0.186 g, 1.67 mmol) and sodium acetate (0.151 g, 1.84 mmol) in 10 mL of water and stirred at rt for 7.5 h. It was then cooled down in an ice-bath for 15 min. The reaction mixture was filtered over a sintered disc Büchner funnel and the solid washed with 5 mL of ice–cold water to give 0.200 g of crude pivalaldehyde semicarbazone which was recrystallized from 5 mL of hot water to give 0.160 g (77%) of pure product, mp 186–188 °C (reported[37] mp 191 °C). TLC, IR, and MS were identical with those of an authentic sample prepared from pivalaldehyde and semicarbazide hydrochloride.

To the filtrate was added $NaHCO_3$ until pH=8 and stirred for 1 h at 0 °C. It was then filtered to give 0.135 g (61%) of pure adamantanamine, mp 203–205 °C. TLC, IR, and MS were identical with those of an authentic sample of adamantanamine (Aldrich).

4.1.21. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with 1 equiv. of trifluoroacetic acid. *tert*-Butyl ammonium trifluoroacetate (15d). Dropwise over a period of 5 min, a solution of trifluoroacetic acid (0.650 g, 5.7 mmol) in 5 mL of THF was added to a solution of 1,3-di-*tert*-butylaziridinone (**5d**) (0.96 g, 5.7 mmol) in 15 mL of THF at 0 °C. The solution stirred for 3 h slowly reaching a temperature of 10 °C and then the THF was removed under reduced pressure to give 1.22 g of a white solid. It was recrystallized from hot *n*-heptane/isopropyl alcohol (3 mL/1 mL) to give 0.87 g (82%) of *tert*-butyl ammonium trifluoroacetate (**15d**), mp 185–187 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 9H), 8.04 (bs, 3H). ^{13}C NMR (DMSO-d_6) δ 27.0, 50.8, 117.1 (q, *J*=299.0 Hz), 158.6 (q, *J*=31.6 Hz). MS: *m/z* 97, 69, 58, 45. Anal. Calcd for $C_6H_{12}F_3NO_2$: C, 38.50; H, 6.42; F, 30.48; N, 7.49. Found: C, 38.67; H, 6.49; F, 30.75; N, 7.47.

4.1.22. *tert*-Butyl ammonium trifluoroacetate (15d). To a solution of *tert*-butylamine (1.76 g, 0.024 mol) in 27 mL of THF is added trifluoroacetic acid (2.96 g, 0.026 mol) in one portion at rt. It is stirred for 17 h then evaporated to dryness to give 3.8 g of a white solid. It was recrystallized from *n*-heptane/isopropyl alcohol (24 mL/7 mL) to give 3.2 g (71%) of a white solid (**15d**), mp 187–189 °C. ^{1}H NMR (DMSO-d_6) δ 1.26 (s, 9H), 8.04 (bs, 3H). ^{13}C NMR (DMSO-d_6) δ 27.0, 50.8, 117.1 (q, *J*=299.0 Hz), 158.6 (q, *J*=31.6 Hz). MS: *m/z*. 97, 69, 58, 45.

4.1.23. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with 2 equiv. of trifluoroacetic acid. *N*-*tert*-Butyl-2,2-dimethyl-1-(trifluoroacetyloxy)propan-1-aminium trifluoroacetate (16). Dropwise, a solution of trifluoroacetic acid (0.91 g, 0.008 mol) in 10 mL of benzene was added to a solution of 1,3-di-*tert*-butylaziridinone (**5d**) (0.68 g, 0.004 mol) in 5 mL of benzene at 10 °C. The resulting mixture was stirred overnight and then filtered to yield pure **16** (74%), mp 119–120 °C. IR (KBr) ν: 2990, 1785, 1691, 1485 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 9H), 1.36 (s, 9H), 4.78 (s, 1H), 8.33 (s, 2H, exchangeable in D_2O). ^{13}C NMR ($CDCl_3$) δ 23.8, 25.5, 36.4, 51.0, 60.9, 115.1 (q, *J*=291.0 Hz), 161.3 (q, *J*=36.0 Hz), 182.9. Anal. Calcd for $C_{13}H_{21}F_6NO_4$: C, 42.28; H, 5.73; F, 30.87; N, 3.79; O, 17.33. Found: C, 42.42; H, 5.73; N, 3.77.

4.1.24. Reaction of 1,3-di-*tert*-butylaziridinone (5d) with trifluoroacetic acid followed by hydrolysis. To 0.611 g (3.6 mmol) of 1,3-di-*tert*-butylaziridinone in 20 mL of benzene is added a solution of trifluoroacetic acid (0.912 g, 8 mmol) in 10 mL of benzene and is stirred at rt for 3 days (immediately upon addition of trifluoroacetic acid gas

evolution was observed). The benzene was removed under reduced pressure to yield a solid to which 6 mL of hexane was added and the mixture was stored at −20 °C for overnight. The precipitate was then filtered to give 0.97 g of a white solid, which was subsequently added to a solution of semicarbazide hydrochloride (0.491 g, 4.4 mmol) and sodium acetate (0.397 g, 4.84 mmol) in 20 mL of water and stirred at rt for 2 days. It was then cooled down in an ice-bath for 15 min. The reaction mixture was filtered over a sintered disc Büchner funnel and the solid washed with 5 mL of ice–cold water to give 0.270 g (52%) of pure pivalaldehyde semicarbazone, mp 186–188 °C. TLC, IR, and MS were identical with those of an authentic sample prepared directly from authentic pivalaldehyde and semicarbazide hydrochloride. No effort was made to isolate the other hydrolysis product, *tert*-butylamine.

4.1.25. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with maleic acid. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (12a). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.317 g, 2.25 mmol) in 17 mL of toluene at 0 °C was added 0.130 g (1.125 mmol) of maleic acid in 15 mL of THF. The solution was stirred for 15 h slowly coming to rt. The solvents were evaporated under reduced pressure and the residue was taken up into 50 mL of methylene chloride and washed with 3×30 mL of 5% $NaHCO_3$ and 2×30 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.36 g of a white solid. After flash chromatography (60% *n*-hexane/40% ethyl acetate), 0.33 g (73%) of a white solid (**12a**) with mp 148–149 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.36. IR (CCl_4) ν: 3448, 3401, 2973, 1731, 1687, 1642 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (s, 18H), 1.61 (s, 12H), 6.26 (s, 2H), 6.30 (bs, 2H, exchangeable in TFD). ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6, 51.2, 83.2, 130.2, 163.4, 171.3. MS: *m*/*z* 398, 383, 343, 326, 299, 256, 228, 160, 143 (base peak), 114, 87, 58, 57, 41.

4.1.26. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with maleic acid. Di[2-methyl-*N*-(1-adamantyl) propanamido-2-]maleate (12b). To a solution of crude 1-(1-adamantyl)-3,3-dimethylaziridinone (0.366 g, 1.67 mmol) in 25 mL of benzene at rt was added 0.097 g (0.835 mmol) of maleic acid in 8 mL of THF. The solution was stirred for 20 h and the solvents were evaporated under reduced pressure to give an oil which was taken up into 60 mL of benzene and washed with 3×30 mL of 5% $NaHCO_3$ and 2×30 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.47 g of a white solid. After flash chromatography (75% *n*-hexane/25% ethyl acetate), 0.39 g (84%) of a white solid (**12b**) with mp 205–206 °C was obtained. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.33. IR (CCl_4) ν: 3439, 3394, 2910, 2852, 1732, 1684, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (s, 12H), 1.68 (s, 12H), 2.02 (s, 12H), 2.07 (s, 6H), 6.16 (s, 2H, exchangeable in D_2O), 6.24 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.5, 36.4, 41.3, 52.0, 83.1, 130.2, 163.3, 171.1. Anal. Calcd for $C_{32}H_{46}N_2O_6$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.26; H, 8.27; N, 4.93.

4.1.27. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone with succinic acid. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)succinate (13a). To a solution of crude 1-*tert*-butyl-3,3-dimethylaziridinone (0.317 g, 2.25 mmol) in 25 mL of toluene at 0 °C was added 0.133 g (1.12 mmol) of succinic acid in 6 mL of THF. The solution was stirred overnight slowly coming to rt for 19 h then was washed with 4×35 mL of 5% $NaHCO_3$ and 2×35 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 0.40 g of an oil which crystallized upon standing. After flash chromatography (65% *n*-hexane/35% ethyl acetate), 0.29 g (65%) of a white solid (**13a**) with mp 106–108 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.34. IR (CCl_4) ν: 3446, 3402, 2966, 2929, 1745, 1686, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 18H), 1.59 (s, 12H), 2.62 (s, 4H), 5.94 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.6, 29.7, 51.1, 82.2, 170.6, 171.9. MS: *m*/*z* 401, 385, 345, 301, 242, 228, 215, 187, 160, 142, 114, 101, 86, 69, 59, 58, 57, 41. Anal. Calcd for $C_{20}H_{36}N_2O_6$: C, 59.98; H, 9.06; N, 6.99. Found: C, 60.03; H, 9.08; N, 6.90.

4.1.28. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) and succinic acid. Di[2-methyl-1-(1-adamantyl)propanamido-2-]succinate (13b). To a solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**) (0.48 g, 0.002 mol) in 15 mL of THF at 0 °C, succinic acid (0.12 g, 0.001 mol) was added. The solution stirred for 7.5 h. THF was removed under reduced pressure. The residue was dissolved in methylene chloride (30 mL) and washed with 5% $NaHCO_3$ (15 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude di[2-methyl-1-(1-adamantyl)propanamido-2]succinate (**13b**) (68.5%). After washing with hot *n*-heptane and ethyl acetate, a white solid with mp 216–218 °C was obtained. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.34. IR (CCl_4) ν: 3420, 2900, 2838, 1735, 1678 cm^{-1}. (KBr) ν: 3390, 2900, 2840, 1730, 1663 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.55 (s, 12H), 1.64 (s, 12H), 1.97 (s, 12H), 2.04 (s, 6H), 2.58 (s, 4H), and 5.76 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 24.7, 29.6, 29.8, 36.5, 41.4, 51.9, 82.2, 170.7, 171.8. Anal. Calcd for $C_{32}H_{48}N_2O_6$: C, 69.04; H, 8.69; N, 5.03. Found: C, 68.90; H, 8.80; N, 5.15.

4.1.29. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone with succinic acid. Di[3,3-dimethyl-1-(1-adamantyl)butanamido-2-]succinate (13c). To a solution of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**) (1.63 g, 0.0066 mol) in 20 mL of dioxane succinic acid (0.35 g, 0.003 mol) was added. The solution was refluxed for 10 h. Dioxane was removed under reduced pressure and the residue was taken up into 25 mL of ethyl acetate and washed with 5% $NaHCO_3$ (20 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford 0.81 g (44%) of crude **13c** which was recrystallized twice from isopropyl alcohol (17 and 11 mL) to give 0.22 g (12.0%) of a white solid (**13c**) with mp 244–246 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.58. IR (CCl_4) ν: 3420, 2900, 2840, 1735, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.7 and 2.0 (s, 30H), 2.65 (s, 4H), and 4.65 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.1, 29.6, 34.1, 36.5, 41.6, 52.2, 81.8, 167.0, 171.3. High resolution MS: *m*/*z* 612, 556, 500, 435, 379, 347, 321, 264, 209, 135 (base peak), 107, 79, 57. Anal. Calcd for $C_{36}H_{56}N_2O_6$: C, 70.55; H, 9.21; N, 4.57. Found: C, 70.34; H, 9.27; N, 4.39.

4.1.30. Reaction of 1,3-di-*tert*-butylaziridinone with succinic acid. Di(3,3-dimethyl-1-*tert*-butylbutanamido-2-)succinate (13d). To a solution of 1,3-di-*tert*-butylaziridinone (**5d**) (2.99 g, 0.0177 mol) in 30 mL of THF, succinic acid (0.95 g, 0.008 mol) was added. The solution was refluxed for 6 h. Dioxane was removed under reduced pressure and the residue was taken up into 40 mL of ethyl acetate and washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford 1.89 g (51.8%) of crude **13d** which was recrystallized from 12 mL of hexane/ethyl acetate. It was filtered and the filtrate was evaporated to give 1.35 g of a sticky solid which was recrystallized twice from *n*-heptane to give 0.89 g (24.4%) of solid **13d** with mp 156–157 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3443, 2967, 2876, 1746, 1686 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.32 (s,18H), 2.7 (s, 4H), 4.6 (s, 2H), and 5.65 (s, 2H).

4.2. Passerini reactions

4.2.1. Passerini reaction between acetic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-acetoxy-2-methylpropanamide (4a). To a solution of acetic acid (1.80 g, 0.03 mol) in acetone (10 mL), *tert*-butyl isonitrile (2.49 g, 0.03 mol) was added. The solution was seeded with *p*-toluene sulfonic acid and sat overnight. The excess acetone was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate removed under reduced pressure to afford crude **4a** (3.03 g, 75.2%). After recrystallization from 10 mL *n*-heptane, a white solid (2.66 g, 66%) with mp 78–79 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.42. IR (CCl_4) ν: 3430, 2955, 1739, 1680, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.30 (s, 9H), 1.55 (s, 6H), 2.02 (s, 3H), and 5.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 22.1, 24.4, 51.1, 81.8, 169.2, 172.2. MS: *m*/*z* 201, 186, 158, 144, 129, 115, 102, 101, 88, 86, 61, 59, 58, 57, 43 (base peak). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.76; H, 9.53; N, 6.96.

4.2.2. Passerini reaction between pivalic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4b). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol), pivalic acid (2.04 g, 0.02 mol), and a catalytic amount of *p*-toluene sulfonic acid in 10 mL of acetone was stirred overnight at room temperature. The excess acetone was removed under reduced pressure and the remaining residue was dissolved in 20 mL of methylene chloride. This solution was washed with 5% $NaHCO_3$ (20 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4b** (2.20 g, 45.2%), a light yellow oil which crystallized upon standing. After recrystallization from 3.5 mL of *n*-heptane, a white solid with mp 50–51 °C was obtained. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.40. IR (CCl_4) ν: 3430, 2960, 1730, 1680, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.31 (s, 9H), 1.55 (s, 6H), 5.82 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.1, 28.6, 39.1, 50.8, 81.6, 172.4, 176.3. MS: *m*/*z* 243, 228, 186, 185, 171, 158, 144, 114, 103, 102, 86, 85, 59, 58, 57 (base peak), 41. Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.35; N, 5.76. Found: C, 64.34; H, 10.48; N, 5.76.

4.2.3. Passerini reaction between benzoic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-benzoyloxy-2-methylpropanamide (4c). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol), benzoic acid (2.44 g, 0.02 mol), and a catalytic amount of *p*-toluene sulfonic acid in 10 mL of acetone was stirred overnight at room temperature. The excess acetone was removed under reduced pressure and the remaining residue was dissolved in 30 mL of ethyl acetate. This solution was washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford crude **4c** (5.27 g, 100%). After recrystallization from 5 mL of carbon tetrachloride, a white solid (1.63 g, 30.9%) with mp 88–89 °C was obtained. The mother liquor was evaporated to yield 2.40 g (45.5%) of a nearly pure second crop with mp 80–84 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3435, 3050, 2955, 1722, 1680, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 1.72 (s, 6H), 5.89 (s, 1H), 7.44 (t, 2H, *J*=7.7 Hz), 7.56 (t, 1H, *J*=7.5 Hz), 7.97 (d, 2H, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 24.7, 28.8, 51.2, 82.5, 128.7, 129.6, 130.7, 133.4, 164.9, and 172.3. MS: *m*/*z* 263, 205, 191, 164, 146, 123, 105 (base peak), 77, 59, 57. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.37; H, 7.98; N, 5.27.

4.2.4. Passerini reaction between *trans*-cinnamic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4d). To a solution of *trans*-cinnamic acid (1.00 g, 0.00675 mol) in an excess amount of acetone (10 mL), *tert*-butyl isonitrile (0.561 g, 0.00675 mol) dissolved in 2 mL of acetone was added dropwise at room temperature. The reaction mixture was stirred for 6 days. The excess acetone and unreacted *tert*-butylisonitrile were removed under reduced pressure. The residue was dissolved in 30 mL of methylene chloride, washed with 2×30 mL of 5% $NaHCO_3$, 3×50 mL of distilled water, the organic layer dried with Na_2SO_4, and the methylene chloride was removed under pressure to yield 1.06 g (54.3%) of **4d**, mp 96–98 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4): 3446, 3085, 3064, 3030, 2950, 1720, 1693, 1635. ^1H NMR ($CDCl_3$): δ 1.37 (s, 9H), 1.68 (s, 6H), 5.86 (bs, 1H), 6.42 (d, *J*=16.0 Hz, 1H), 7.40–7.53 (m, 5H), 7.67 (d, *J*=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.7, 51.0, 81.9, 118.3, 128.2, 129.0, 130.5, 134.2, 145.4, 165.1, 172.2. MS: *m*/*z* 231, 217, 190, 175, 172, 145, 131 (base peak), 103, 77, 59, 57, 51, 41.

4.2.5. Passerini reaction between trifluoroacetic acid, acetone, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-methyl-2-trifluoroacetoxypropanamide (4e). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 5 mL of acetone was added dropwise to a solution of trifluoroacetic acid (3.42 g, 0.03 mol) in 10 mL of acetone at −10 °C over a period of 10 min. The ice-bath was then removed and the solution stirred at rt for 2 days. Excess acetone was evaporated under reduced pressure to yield 6.36 g of a light yellow oil which was taken up into 30 mL of ethyl acetate and washed with 30 mL of 5% $NaHCO_3$, 2×20 mL of distilled water, dried with Na_2SO_4, filtered and rotary evaporated to give 3.30 g (64.7%) of a light yellow oil which solidified after 3 days. It

was purified by vacuum sublimation (40–50 °C at 11 mm) to give 2.4 g (47%) of a white solid **4e**, mp 45–46 °C. TLC (90% *n*-hexane/10% isopropyl alcohol) R_f=0.45. IR (CCl_4) ν: 3454, 2970, 1793, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.35 (s, 9H), 1.70 (s, 6H), 5.85 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.7, 28.5, 51.5, 87.0, 114.3 (q, J=286.5 Hz), 155.0 (q, J=42.0 Hz), 169.9. MS: *m/z* 255, 240, 184, 155, 126, 114, 98, 86, 69, 57 (base peak), **41**. Anal. Calcd for $C_{10}H_{16}F_3NO_3$: C, 47.06; H, 6.32; N, 5.49. Found: C, 47.32; H, 6.51; N, 5.57.

4.2.6. Passerini reaction between acetic acid, acetone and adamantyl isonitrile. *N*-(1-Adamantyl)-2-acetoxy-2-methylpropanamide (4f). To a solution of acetic acid (0.405 g, 0.00675 mol) in an excess amount of acetone (10 mL), adamantyl isonitrile (1.09 g, 0.00675 mol) dissolved in 10 mL of acetone was added dropwise at room temperature. The reaction mixture was stirred for 5 days. The excess acetone was removed under reduced pressure. The residue was dissolved in 30 mL of methylene chloride, washed with 2×30 mL of 5% $NaHCO_3$, 3×50 mL of distilled water, the organic layer dried with Na_2SO_4, and the methylene chloride was removed under reduced pressure to yield 0.93 g (49.5%) of pure **4f**, mp 154–156. TLC (90% ethyl acetate/10% hexane) R_f=0.20. IR (CCl_4): 3403, 2920, 2854, 1750, 1688. ^1H NMR ($CDCl_3$): δ 1.59 (s, 6H), 1.69 (s, 6H), 2.00 (s, 6H), 2.07 (s, 6H), 5.67 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ 22.0, 24.3, 29.5, 36.4, 41.4, 51.6, 81.7, 169.1, 171.9. MS: *m/z* 279, 236, 222, 219, 178, 176, 150, 135 (base peak), 102, 93, 79, 59, 43, 41.

4.2.7. Passerini reaction between pivalic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-(2,2-dimethylpropanoyloxy)-2-methylpropanamide (4g). To a solution of pivalic acid (0.633 g, 0.0062 mol) in an excess amount of acetone (20 mL), adamantyl isonitrile (1.00 g, 0.0062 mol) dissolved in 10 mL of acetone was added dropwise at room temperature over a period of 10 min. A catalytic amount of *p*-toluenesulfonic acid was added and the reaction was stirred for 7 days. The excess acetone was removed under reduced pressure. The residue was dissolved in 50 mL of methylene chloride, washed with 4×30 mL of 5% $NaHCO_3$, 3×30 mL of distilled water, dried with Na_2SO_4, and the methylene chloride was removed under reduced pressure to yield 1.14 g of a yellow solid. It was flash chromatographed (92.5% *n*-hexane/7.5% ethyl acetate) to give a white solid (**4g**) 0.57 g (28.6%), mp 63–65 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.32. IR (CCl_4) ν: 3438, 2910, 2852, 1739, 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (s, 9H), 1.59 (s, 6H), 1.69 (s, 6H), 1.99 (s, 6H), 2.08 (s, 3H), 5.75 (bs, 1H, exchangeable in D_2O). ^{13}C NMR ($CDCl_3$): δ 24.1, 27.2, 29.5, 36.4, 39.1, 41.5, 51.4, 81.6, 172.2, 176.3. MS: *m/z* 321, 306, 263, 236, 219, 220, 192, 163, 150, 144, 135 (base peak), 107, 103, 93, 85, 79, 67, 59, 57, 41.

4.2.8. Passerini reaction between benzoic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-benzoyloxy-2-methylpropanamide (4h). To a solution of 0.460 g (0.00377 mol) benzoic acid in an excess of acetone (3 mL), 0.600 g (0.00372 mol) of adamantyl isonitrile dissolved in 2 mL of acetone was added dropwise at room temperature. The reaction mixture was stirred for 4 days. The excess acetone was removed under reduced pressure and the residue was dissolved in 30 mL of ethyl acetate, washed with 5% $NaHCO_3$ (30 mL) and distilled water (2×20 mL), dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford 0.87 g (68.5%) of a white solid. It was flash chromatographed (90% *n*-hexane/10% ethyl acetate) to give 0.41 g (32.3%) of a white solid (**4h**), mp 101–103 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.24. IR (CCl_4): ν=3441, 2910, 2852, 1730, 1686. ^1H NMR ($CDCl_3$): δ 1.68 (s, 6H), 1.73 (s, 6H), 2.02 (s, 6H), 2.08 (s, 3H), 5.78 (bs, 1H, exchangeable in D_2O), 7.47 (t, 2H, J=7.0 Hz, 8.0 Hz), 7.59 (t, 1H, J=7.0 Hz), 8.00 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$): δ 24.6, 29.5, 36.4, 41.5, 51.7, 82.3, 128.5, 129.5, 130.7, 133.2, 164.8, 171.9. MS: *m/z* 341, 283, 240, 219, 193, 192, 191, 164, 135 (base peak), 105, 77, 59.

4.2.9. Passerini reaction between *trans*-cinnamic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-methyl-2-(*trans*-3-phenylacryloyloxy)propanamide (4i). To a solution of *trans*-cinnamic acid (0.919 g, 0.0062 mol) in an excess amount of acetone (25 mL), adamantyl isonitrile (1.00 g, 0.0062 mol) in 25 mL of acetone was added dropwise over a period of 10 min at room temperature. A catalytic amount of *p*-toluenesulfonic acid was added and the reaction mixture was stirred for 7 days. The excess acetone was removed under reduced pressure and the residue was dissolved in 90 mL of methylene chloride, washed with 3×40 mL of 5% $NaHCO_3$, 2×30 mL of distilled water. The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to yield 1.36 g of crude **4i**. After flash chromatography (90% *n*-hexane/10% ethyl acetate), 0.52 g (22.8%) of a white solid (**4i**) with mp 124–125 °C was obtained. 0.30 g of pure unreacted adamantyl isonitrile was also recovered. TLC (85% *n*-hexane/15% ethyl acetate) R_f=0.39. IR (CCl_4) ν: 3438, 3064, 3029, 2910, 2851, 1722, 1686, 1637 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.68 (s, 12H), 2.03 (s, 6H), 2.08 (s, 3H), 5.74 (bs, 1H, exchangeable in D_2O), 6.42 (d, 1H, J=16.0 Hz), 7.40 (s, 3H), 7.53 (s, 2H), 7.68 (d, 1H, J=16.0 Hz). ^{13}C NMR ($CDCl_3$): δ 25.0, 29.8, 36.7, 41.8, 52.0, 82.2, 118.7, 128.5, 129.3, 130.9, 134.6, 145.7, 165.5, 172.3. MS: *m/z* 367, 309, 238, 219, 190, 175, 150, 145, 135 (base peak), 131, 107, 103, 93, 91, 79, 77, 59, 41.

4.2.10. Passerini reaction between trifluoroacetic acid, acetone, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-methyl-2-trifluoroacetoxypropanamide (4j). Dropwise, a solution of adamantyl isonitrile (1.61 g, 0.01 mL) in 20 mL of methylene chloride was added to a solution of trifluoroacetic acid (1.14 g, 0.01 mol) in 5 mL of acetone. The solution was stirred overnight. Methylene chloride and excess acetone was removed under reduced pressure. The residue was taken up in methylene chloride, washed with 5% $NaHCO_3$ (40 mL) and distilled water (2×20 mL). The organic layer was dried with Na_2SO_4, and the methylene chloride was removed under reduced pressure to afford **4j** (2.51 g, 75.4%). An analytical sample was obtained by vacuum sublimation (50–60 °C at 0.5 mm), mp 98–99 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.42. IR (CCl_4) ν: 3445, 2911, 2852, 1792, 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.67 (t, 6H, J=2.7 Hz), 1.70 (s, 6H), 1.97 (d, 6H, J=2.7 Hz), 2.08 (s, 3H), 5.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 29.6,

36.4, 41.5, 52.2, 87.0, 114.4 (q, J=287.0 Hz), 155.4 (q, J=42.4 Hz) 169.7. MS: m/z 333, 219, 192, 176, 155, 135 (base peak), 107, 93, 69, 41. Anal. Calcd for $C_{16}H_{22}F_3NO_3$: C, 57.65; H, 6.65; N, 4.20. Found: C, 57.43; H, 6.67; N, 4.28.

4.2.11. Passerini reaction between acetic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-acetoxy-3,3-dimethylbutanamide (4k). Dropwise, at 0 °C, a solution of adamantyl isonitrile (1.61 g, 0.01 mol) in 15 mL of THF was added to a solution of acetic acid (0.600 g, 0.01 mol) and pivalaldehyde (0.861 g, 0.01 mol) in 20 mL of THF. After the addition of the isonitrile, the ice bath was removed and the solution was stirred for 5 days at rt. THF was removed under reduced pressure and the resulting residue was dissolved in 35 mL of ethyl acetate. The solution was washed with 5% $NaHCO_3$ (15 mL) and distilled water (15 mL). The organic layer was dried with Na_2SO_4 and the ethyl acetate was removed under reduced pressure to afford crude **4k** (2.74 g, 89.3%). Purification by flash chromatography (90% *n*-hexane/10% ethyl acetate) yielded pure **4k** (1.76 g, 57.3%), mp 140–141 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.25. IR (CCl_4) ν: 3437, 2911, 2852, 1752, 1691, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (s, 9H), 1.64 (m, 6H), 1.97 (m, 6H), 2.04 (s, 3H), 2.11 (s, 3H), 4.63 (s, 1H), and 5.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.7, 29.8, 32.0, 34.4, 36.7, 42.0, 52.3, 81.5, 167.6, 170.1. MS: m/z 307, 251, 232, 207, 178, 150, 135 (base peak), 120, 93, 79, 57, 43. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 70.39; H, 9.55; N, 4.51.

4.2.12. Passerini reaction between pivalic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4l). Dropwise, at 0 °C, a solution of adamantyl isonitrile (0.806 g, 0.005 mol) in 10 mL of THF was added to a solution of pivalic acid (0.511 g, 0.005 mol) and pivalaldehyde (0.431 g, 0.005 mol) in 10 mL of THF. After the addition of the isonitrile, the ice bath was removed and the solution was stirred for 6 days at rt. THF was removed under reduced pressure and the resulting residue was dissolved in 15 mL of methylene chloride. The solution was washed with 5% $NaHCO_3$ (15 mL) and distilled water (2×10 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4l** (1.30 g, 74.3%). After recrystallization from 8 mL of *n*-hexane, 0.95 g (54.4%) of a white solid with mp 88–89 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.63. IR (CCl_4) ν: 3437, 2910, 1743, 1689, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.02 (s, 9H), 1.26 (s, 9H), 1.67 (s, 6H), 1.98 (s, 6H), 2.07 (s, 3H), 4.68 (s, 1H), 5.48 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 27.2, 29.4, 34.2, 36.3, 38.9, 41.6, 51.8, 80.6, 167.6, 176.5. MS: m/z 349, 293, 249, 232, 208, 172, 163, 135 (base peak), 117, 85, 70, 57. Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.28; H, 10.15; N, 3.93.

4.2.13. Passerini reaction between benzoic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-2-benzoyloxy-3,3-dimethylbutanamide (4m). Adamantyl isonitrile (1.61 g, 0.01 mol) was added to a solution of benzoic acid (1.22 g, 0.01 mol) and pivalaldehyde (0.861 g, 0.01 mol) in 20 mL of CH_2Cl_2 at rt and stirred for 2 days. The solution was washed with 5% $NaHCO_3$ (25 mL) and distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and the CH_2Cl_2 was removed under reduced pressure to afford crude **4m** (2.80 g, 75.7%). Recrystallization from *n*-heptane/ethyl acetate (20 mL/3 mL) yielded 2.50 g (67.6%) of pure **4m**, mp 166–168 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.67. IR (CCl_4) ν: 3436, 2911, 2852, 1734, 1688, 1513 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.14 (s, 9H), 1.66 (s, 6H), 1.99 (s, 6H), 2.06 (s, 3H), 4.93 (s, 1H), 5.55 (s, 1H), 7.48 (m, 2H), 7.63 (m, 1H), 8.10 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.4, 34.4, 36.3, 41.6, 52.0, 81.5, 128.7, 133.4, 165.2, 167.2. MS: m/z 369, 313, 283, 269, 240, 208, 192, 177, 135 (base peak), 105, 79, 77, 70. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.66; H, 8.49; N, 3.77.

4.2.14. Passerini reaction between *trans*-cinnamic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4n). Dropwise, at 0 °C, a solution of adamantyl isonitrile (1.61 g, 0.01 mol) in 20 mL of THF was added to a solution of *trans*-cinnamic acid (1.48 g, 0.01 mol) and pivalaldehyde (0.861 g, 0.01 mol) in 20 mL of THF. After the addition of the isonitrile, the ice bath was removed and the solution was stirred for 6 days. THF was removed under reduced pressure and the resulting residue was dissolved in 25 mL of methylene chloride. The solution was washed with 5% $NaHCO_3$ (15 mL) and distilled water (2×10 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4n** (3.54 g, 89.4%). After recrystallization from 22 mL of *n*-hexane, 2.97 g (75%) of a white solid with mp 122–123 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.52. IR (CCl_4) ν: 3429, 3060, 2910, 1732, 1687, 1638, 1549, 1512 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.07 (s, 9H), 1.67 (s, 6H), 2.00 (s, 6H), 2.07 (s, 3H), 4.82 (s, 1H), 5.54 (bs, 1H), 6.50 (d, J=16.0 Hz, 1H), 7.44 (m, 3H), 7.55 (dd, J=3.7 Hz, 2H), 7.76 (d, J=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 29.4, 34.2, 36.3, 41.6, 52.0, 81.1, 117.2, 128.3, 129.1, 130.7, 134.1, 146.0, 165.7, 167.3. MS (ES): m/z 417.9 (M+23), 395.8, 380.9, 313.1, 245.0. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.75; H, 8.40; N, 3.52.

4.2.15. Passerini reaction between trifluoroacetic acid, pivalaldehyde, and adamantyl isonitrile. *N*-(1-Adamantyl)-3,3-dimethyl-2-trifluoroacetoxybutanamide (4o). A solution of pivaldehyde (0.43 g, 0.005 mol) in 2 mL of methylene chloride was added to a solution of trifuoroacetic acid (0.57 g, 0.005 mol) in 10 mL of methylene chloride dropwise. A solution of adamantyl isonitrile (0.805 g, 0.005 mol) was added dropwise, to the mixture at −10 °C. The solution stirred for 4 days and the mixture was filtered. It was washed with 30 mL of 5% $NaHCO_3$, 2×20 mL H_2O, dried with Na_2SO_4, and evaporated under reduced pressure to give an oil (1.42 g, 79%) which solidified upon standing. Crude **4o** was recrystallized from 2 mL *n*-heptane to give 1.26 g (69.6%) of pure **4o**, mp 108–111 °C. TLC (90% *n*-hexane/10% ethyl acetate): R_f=0.78. IR (CCl_4) ν: 3437, 2912, 1796, 1693 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.96 and 1.04 (s, 9H), 1.66 (s, 12H), 1.99 (s, 3H), 4.82 (s, 1H), 5.46 (s, 1H, exchanges in TFD). ^{13}C NMR ($CDCl_3$) δ 26.1, 29.5, 34.5,

36.4, 41.6, 52.8, 84.5, 115.0 (q, J=287.0 Hz), 156.4 (q, J=43.0 Hz), 165.4. MS: m/z 361, 343, 305, 292, 268, 232, 208, 193, 176, 135 (base peak), 107, 79, 69, 41. Anal. Calcd for $C_{18}H_{26}F_3NO_3$: C, 59.82; H, 7.25; N, 3.88. Found: C, 59.58; H, 7.30; N, 3.90.

4.2.16. Passerini reaction between acetic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-acetoxy-3,3-dimethylbutanamide (4p). Dropwise, at −15 °C, a solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 10 mL of methylene chloride was added dropwise to a solution of acetic acid (1.20 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 25 mL of methylene chloride over a period of 5 min. After the addition, the ice-bath was removed and the solution stirred overnight at rt. The reaction mixture was washed with 5% $NaHCO_3$ (2×20 mL) and distilled water (20 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4p** (2.75 g, 60.0%). After recrystallization from 3 mL of *n*-hexane, a white solid (1.92 g, 41.9%) with mp 62–63 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.44. IR (CCl_4) ν: 3440, 2965, 1738, 1683, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.98 (s, 9H), 2.11 (s, 3H), 4.64 (s, 1H), 5.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.0, 26.4, 28.8, 34.2, 51.4, 81.2, 167.7, 169.9. MS: m/z 229, 214, 186, 173, 157, 131, 129, 87, 75, 57 (base peak), 43. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.88; H, 10.04; N, 6.11. Found: C, 62.78; H, 10.02; N, 6.21.

4.2.17. Passerini reaction between pivalic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-3,3-dimethyl-2-(2,2-dimethylpropanoyloxy)butanamide (4q). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 5 mL of methylene chloride was added dropwise to a solution of pivalic acid (2.04 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 20 mL of methylene chloride. The solution stirred overnight. The reaction mixture was washed with 5% $NaHCO_3$ (2×25 mL) and distilled water (25 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford 4.39 g (81%) of pure **4q**, mp 87–88 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.48. IR (CCl_4) ν: 3427, 3370, 2955, 2860, 1735, 1667, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.99 (s, 9H), 1.24 (s, 9H), 1.30 (s, 9H), 4.66 (s, 1H), and 5.59 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.5, 27.3, 28.8, 34.4, 39.0, 51.3, 80.8, 167.8, and 176.7. MS: m/z 271, 256, 215, 199, 172, 157, 143, 130, 102, 85, 71, 57 (base peak), 41. Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77; N, 5.16. Found: C, 66.26; H, 10.67; N, 5.24.

4.2.18. Passerini reaction between benzoic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-2-benzoyloxy-3,3-dimethylbutanamide (4r). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 10 mL of methylene chloride was added to a solution of benzoic acid (2.44 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 25 mL of methylene chloride dropwise at −15 °C. After the addition, the ice-bath was removed and the solution stirred overnight at rt. The reaction mixture was washed with 5% $NaHCO_3$ (2×15 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to afford crude **4r** (2.86 g, 49.1%). After recrystallization from 15 mL of carbon tetrachloride, a white solid (1.88 g, 32.3%) with mp 128–129 °C was obtained. The mother liquor was evaporated to yield an additional 0.742 g (12.7%) of a solid with mp 126–127 °C. TLC (90% *n*-hexane/10% ethyl acetate) R_f=0.68. IR (CCl_4) ν: 3440, 3380, 3060, 2965, 2870, 1720, 1685, 1598, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H), 1.32 (s, 9H), 4.91 (s, 1H), 5.70 (s, 1H), 7.47 (m, 2H), 7.59 (m, 1H), 8.09 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.6, 51.4, 81.7, 128.8, 129.8, 133.6, 165.4, 167.6. MS: m/z 291, 276, 253, 235, 219, 192, 177, 143, 130, 105 (base peak), 87, 77, 70, 57, 41. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.27; H, 8.64; N, 4.74.

4.2.19. Passerini reaction between *trans*-cinnamic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-3,3-dimethyl-2-(*trans*-3-phenylacryloyloxy)butanamide (4s). A solution of *tert*-butyl isonitrile (1.66 g, 0.02 mol) in 10 mL of methylene chloride was added dropwise to a solution of *trans*-cinnamic acid (2.96 g, 0.02 mol) and pivalaldehyde (1.72 g, 0.02 mol) in 30 mL of methylene chloride at −15 °C over a period of 10 min. The ice-bath was then removed and the solution stirred overnight at rt. The reaction mixture was washed with 5% $NaHCO_3$ (2×20 mL) and distilled water (2×15 mL). The organic layer was dried with Na_2SO_4 and the methylene chloride was removed under reduced pressure to yield crude **4s** (4.89 g, 77.1%). After recrystallization from *n*-heptane/methylene chloride (10 mL/2 mL), a white solid (2.08 g, 32.8%) with mp 97–98 °C was obtained. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.46. IR (CCl_4) ν: 3440, 2960, 2868, 1715, 1680, 1633, 1505 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.06 (s, 9H), 1.33 (s, 9H), 4.81 (s, 1H), 5.70 (s, 1H), 6.50 (d, 1H, J=16.0 Hz), 7.38 (m, 3H), 7.54 (m, 2H), 7.74 (d, 1H, J=16.0 Hz). ^{13}C NMR ($CDCl_3$) δ 26.6, 28.8, 34.4, 51.4, 81.2, 117.3, 128.4, 129.1, 130.8, 134.2, 146.2, 165.8, 167.7. MS: m/z 317, 261, 245, 231, 218, 175, 162, 149, 131 (base peak), 103, 77, 70, 57, 41. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.92; H, 8.52; N, 4.42. Found: C, 71.77; H, 8.47; N, 4.38.

4.2.20. Passerini reaction between trifluoroacetic acid, pivalaldehyde, and *tert*-butyl isonitrile. *N*-*tert*-Butyl-3,3-dimethyl-2-trifluoroacetoxybutanamide (4t). A solution of *tert*-butyl isonitrile (1.25 g, 0.015 mol) in 15 mL of CH_2Cl_2 was added dropwise to a solution of pivaladehyde (1.29 g, 0.015 mol) and trifluoroacetic acid (1.71 g, 0.015 mol) in 30 mL of CH_2Cl_2 at 0 °C over a period of 15 min. The ice-bath was then removed and the solution stirred at rt for 4 days. The solvents were evaporated under reduced pressure to yield 3.92 g of a white solid which was recrystallized from 20 mL of hot *n*-heptane to give 3.06 g (72%) of a white solid (**4t**), mp 120–121 °C. IR (CCl_4) ν: 3446, 2968, 1796, 1693 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (s, 9H), 1.37 (s, 9H), 4.86 (s, 1H), 5.56 (bs, 1H, exchangeable in TFD). ^{13}C NMR ($CDCl_3$): δ 26.4, 29.0, 34.7, 52.2, 84.9, 114.9 (q, J=285.7 Hz), 156.6 (q, J=42.7 Hz), 165.6. MS: m/z 283, 268, 227, 214, 183, 171, 154, 130, 114, 84, 74, 69, 58, 57, 41. Anal. Calcd for $C_{12}H_{20}F_3NO_3$: C, 50.88; H, 7.12; N, 4.94. Found: C, 51.16; H, 7.18; N, 4.97.

4.2.21. Passerini reaction between maleic acid, acetone, and *tert*-butyl isonitrile. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (12a). To a solution of maleic acid (4.06 g, 0.035 mol) in acetone (70 mL), *tert*-butyl isonitrile (5.82 g, 0.07 mol) was added in one portion at rt. The

solution was seeded with a few crystals of *p*-toluene sulfonic acid and stirred for 3 days. It was then evaporated to dryness under reduced pressure and the residue taken up into 75 mL of CH_2Cl_2 and washed with 3×50 mL of 5% $NaHCO_3$ and 70 mL of H_2O, dried with Na_2SO_4, filtered and evaporated under reduced pressure to give 5.20 g of a brown solid. It was recrystallized from 40 mL of hot *n*-heptane and 1 mL of acetonitrile (to which 0.3 g of activated charcoal was added) to give 3.70 g of a yellow solid, mp 100–120 °C. After flash chromatography (60% *n*-hexane/40% ethyl acetate), 3.23 g (23%) of a white solid, pure **12a** with mp 148–149 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.41. IR (CCl_4) ν: 3448, 3401, 2973, 1731, 1687, 1642 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.36 (s, 18H), 1.61 (s, 12H), 6.26 (s, 2H), 6.30 (bs, 2H, exchangeable in TFD). ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6, 51.2, 83.2, 130.2, 163.4, 171.3. MS: *m/z* 398, 383, 343, 326, 299, 256, 228, 160, 143 (base peak), 114, 87, 58, 57, 41. Anal. Calcd for $C_{20}H_{34}N_2O_6$: C, 60.27; H, 8.60; N, 7.03. Found: C, 60.28; H, 8.87; N, 7.08.

4.2.22. Passerini reaction between maleic acid, acetone, and adamantyl isonitrile. Di[2-methyl-*N*-(1-adamantyl)-propanamido-2-]maleate (12b). To a solution of maleic acid (0.360 g, 0.0031 mol) in acetone (20 mL), adamantyl isonitrile (1.00 g, 0.0062 mol) in 10 mL of acetone was added dropwise over a period of 10 min at rt. The solution was seeded with a few crystals of *p*-toluene sulfonic acid and stirred for 5 days. It was then evaporated to dryness under reduced pressure and the residue taken up into 60 mL of CH_2Cl_2 and washed with 3×25 mL of 5% $NaHCO_3$ and 2×25 mL of H_2O, dried with Na_2SO_4, filtered and evaporated under reduced pressure to give a yellow oil that was flash chromatographed (75% *n*-hexane/25% ethyl acetate) to give 0.40 g (23.3%) of a white solid (**12b**) with mp 205–206 °C was obtained. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.36. IR (CCl_4) ν: 3439, 3394, 2910, 2852, 1732, 1684, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (s, 12H), 1.68 (s, 12H), 2.02 (s, 12H), 2.07 (s, 6H), 6.16 (s, 2H, exchangeable in D_2O), 6.24 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.5, 36.4, 41.3, 52.0, 83.1, 130.2, 163.3, 171.1.

4.2.23. Passerini reaction between succinic acid, acetone, and *tert*-butyl isonitrile. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)succinate (13a). To a solution of succinic acid (2.84 g, 0.002 mol) in acetone (100 mL), *tert*-butyl isonitrile (4.00 g, 0.004 mol) was added in one portion at rt. The solution was seeded with a few crystals of *p*-toluene sulfonic acid and stirred for 3 days. It was then evaporated to dryness under reduced pressure and the residue taken up into 75 mL of CH_2Cl_2 and washed with 3×50 mL of 5% $NaHCO_3$ and 70 mL of H_2O, dried with Na_2SO_4, filtered and evaporated under reduced pressure to give 1.60 g of a white solid mp 88–97 °C. After flash chromatography (60% *n*-hexane/40% ethyl acetate), 1.35 g (14%) of a white solid (**13a**) mp 106–108 °C was obtained. TLC (60% *n*-hexane/40% ethyl acetate) R_f=0.46. ^1H NMR ($CDCl_3$): δ 1.35 (s, 18H), 1.59 (s, 12H), 2.62 (s, 4H), 5.94 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ 24.5, 28.6, 29.7, 51.1, 82.2, 170.6, 171.9. MS: *m/z* 401, 385, 345, 328, 301, 260, 242, 228, 215, 187, 160, 142, 114, 101, 86, 69, 59, 58, 57, 41. Anal. Calcd for $C_{20}H_{36}N_2O_6$: C, 59.98; H, 9.06; N, 6.99. Found: C, 60.14; H, 9.10; N, 6.97.

4.2.24. Passerini reaction between succinic acid, acetone, and adamantyl isonitrile. Di[2-methyl-1-(1-adamantyl)-propanamido-2-]succinate (13b). To a solution of succinic acid (1.18 g, 0.01 mol) in acetone (20 mL) and 5 mL of THF, adamantylisonitrile (3.23 g, 0.02 mol) was added at rt. The solution was seeded with *p*-toluene sulfonic acid and stirred for 5 days. The excess acetone and THF were removed under reduced pressure. The residue was dissolved in methylene chloride (50 mL) and washed with 5% $NaHCO_3$ (20 mL) and distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and methylene chloride removed under reduced pressure to afford crude product **13b** (5.22 g, 93.7%). It was recrystallized twice, first from hot carbon tetrachloride/ acetonitrile (20 mL/ 10 mL) and then from hot *n*-heptane/acetonitrile (18 mL/ 27 mL) to give 1.28 g (23.0%) of a solid with mp 218–221 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3420, 2900, 2838, 1737, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.55 (s, 12H), 1.64 (s, 12H), 1.97 (s, 12H), 2.04 (s, 6H), 2.58 (s, 4H), 5.76 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 24.7, 29.6, 29.8, 36.5, 41.4, 51.9, 82.2, 170.7, 171.8.

4.2.25. Passerini reaction between succinic acid, pivalaldehyde, and adamantyl isonitrile. Di[3,3-dimethyl-1-(1-adamantyl)butanamido-2-]succinate (13c). To a solution of succinic acid (0.59 g, 0.005 mol) and pivalaldehyde (0.86 g, 0.01 mol) in methylene chloride (40 mL) and 10 mL of THF, adamantyl isonitrile (1.61 g, 0.01 mol) was added. The solution was stirred for 5 days. It was then evaporated to dryness under reduced pressure to give a residue which was taken up into 40 mL of methylene chloride. It was washed with 25 mL of 5% $NaHCO_3$, 2×25 mL of H_2O dried with Na_2SO_4 and evaporated under reduced pressure to afford 2.46 g (80.4%) of a dark oil which slowly crystallized. It was flash chromatographed (70% *n*-hexane/30% ethyl acetate) to yield 1.26 g (41.2%) of a solid (**13c**) with mp 243–245 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.58. IR (CCl_4) ν: 3420, 2900, 2840, 1735, 1670 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.7 and 2.0 (s, 30H), 2.65 (s, 4H), and 4.65 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 26.5, 29.1, 29.6, 34.1, 36.5, 41.6, 52.2, 81.8, 167.0, 171.3. High resolution MS: *m/z* 612, 556, 500, 435, 379, 347, 321, 264, 209, 135 (base peak), 107, 79, 57. Anal. Calcd for $C_{36}H_{56}N_2O_6$: C, 70.55; H, 9.21; N, 4.57. Found: C, 70.73; H, 9.27; N, 4.60.

4.2.26. Passerini reaction between succinic acid, pivalaldehyde, and *tert*-butyl isonitrile. Di(3,3-dimethyl-*N*-*tert*-butylbutanamido-2-]succinate (13d). To a solution of succinic acid (2.36 g, 0.02 mol) and pivalaldehyde (3.44 g, 0.04 mol) in methylene chloride (55 mL), *tert*-butyl isonitrile (3.32 g, 0.04 mol) was added at 0 °C. It was seeded with a crystal of *p*-toluene sulfonic acid and stirred for 4 days at rt. It was washed with 40 mL of 5% $NaHCO_3$, 2×25 mL of H_2O, dried with Na_2SO_4 and evaporated under reduced pressure to afford 7.77 g (85.1%) of an oil which slowly crystallized. It was recrystallized twice from *n*-heptane/ethyl acetate to give 2.3 g (25.2%) of a solid (**13d**) with mp 161–162 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.35. IR (CCl_4) ν: 3443, 2967, 2872, 1744, 1687 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.0 (s, 18H), 1.32 (s,18H), 2.7 (s, 4H), 4.6 (s, 2H), and 5.65 (s, 2H). Anal. Calcd for $C_{24}H_{44}N_2O_6$: C, 63.13; H, 9.71; N, 6.13. Found: C, 63.22; H, 9.68; N, 6.27.

4.3. Reactions of α-lactams with maleic anhydride

4.3.1. Reaction of 1-*tert*-butyl-3,3-dimethylaziridinone (5a) with maleic anhydride. Di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (12a). 1-*tert*-Butyl-3,3-dimethylaziridinone (**5a**) (1.41 g, 0.010 mol) was dissolved in 10 mL of chloroform, a solution of freshly sublimed, powdered maleic anhydride (0.98 g, 0.010 mol) in 10 mL of chloroform was added at 0 °C, and the reaction mixture was stirred at 0 °C for 20 h. After evaporation of the solvent on a rotary evaporator, the solid residue was chromatographed on neutral alumina, Woelm, activity grade one, further deactivated by the addition of water (3 mL of water/100 g of alumina) with benzene–methylene chloride as eluent, to afford 1.07 g (53%) of di(2-methyl-*N*-*tert*-butylpropanamido-2-)maleate (**12a**), mp 150–151 °C. IR (CCl_4) ν: 3425, 3370, 1730, 1678, 1525 cm^{-1}. UV: λ_{max} (ethanol)= 200 nm, log ε=4.37. λ_{max} (ethanol) of dimethyl maleate= 192.5 nm, log ε=4.34.[37] ^1H NMR ($CDCl_3$) δ 1.39 (s, 18H), 1.65s, (12H), 4.80 (s, 1H), 6.39 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.6, 28.6, 51.2, 83.2, 130.2, 163.4, 171.3. MS: *m/z* 398, 383, 343, 326, 299, 256, 228, 160, 143 (base peak), 114, 87, 58, 57, 41. Anal. Calcd for $C_{20}H_{34}N_2O_6$: C, 60.27; H, 8.60; N, 7.03. Found: C, 60.18; H, 8.41; N, 7.16.

Using a relative ratio of 4 equiv. of α-lactam to 1 equiv. of maleic anhydride, and a reaction time of 48 h at room temperature, increased the isolated yield of **12a**, after chromatography, to 87%.

4.3.2. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with maleic anhydride. Di[2-methyl-*N*-(1-adamantyl)propanamido-2-]maleate (12b). A solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (**5b**) (1.15 g, 5.25 mmol) and freshly sublimed maleic anhydride (0.515 g, 5.25 mmol) in 25 mL of carbon tetrachloride was heated to 70 °C for 10 min. It was then washed with 2×25 mL of 2 N HCl, 2×25 mL of H_2O, dried with Na_2SO_4, filtered over Celite, and rotary evaporated to give 1.28 g of a purple solid, which was flash chromatographed (75% *n*-hexane/25% ethyl acetate) to give 0.25 g (17.1%) of di[2-methyl-*N*-(1-adamantyl)propanamido-2-]maleate (**12b**), mp 204–206 °C. TLC (70% *n*-hexane/30% ethyl acetate) R_f=0.36. IR (CCl_4) ν: 3439, 3394, 2910, 2852, 1732, 1684, 1635 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.61 (s, 12H), 1.68 (s, 12H), 2.02 (s, 12H), 2.07 (s, 6H), 6.16 (s, 2H, exchangeable in D_2O), 6.24 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 24.7, 29.5, 36.4, 41.3, 52.0, 83.1, 130.2, 163.3, 171.1.

0.22 g (26%) of pure adamantyl isonitrile was also isolated from the reaction and approximately 51% of a purple dye remained on the column.

4.4. Reactions of α-lactams with mineral acids

4.4.1. Reaction of 1-(1-adamantyl)-3,3-dimethylaziridinone (5b) with hydrofluoric acid. *N*-(1-Adamantyl)-2-fluoro-2-methylpropanamide (4u). To a solution of 1-(1-adamantyl)-3,3-dimethylaziridinone (0.737 g, 0.0034 mol) in 45 mL of benzene at 7 °C, 5 mL (0.175 mol) of HF/pyridine complex was added. The solution was stirred for 1.5 h, then washed with distilled water (2×25 mL), 2 N HCl (10 mL), and again with distilled water (2×25 mL). The organic layer was dried with Na_2SO_4 and the benzene was removed under reduced pressure to afford crude *N*-(1-adamantyl)-2-fluoro-2-methylpropanamide (**4u**) (0.55 g, 67.6%). After column chromatography, pure **4u** was obtained (0.42 g, 51.6%), mp 42–44 °C. TLC (80% *n*-hexane/20% ethyl acetate) R_f=0.65. IR (CCl_4) ν: 3420, 2960, 2900, 2840, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.51 (s, 6H), 1.65 (s, 6H), 1.98 (d, *J*=2.7 Hz, 6H), 2.05 (s, 3H), 6.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.1 (d, *J*=23.8 Hz), 29.6, 36.5, 41.6, 51.7, 96.3 (d, *J*=181.6 Hz), 172.3 (d, *J*=19.2 Hz). MS: *m/z* 239, 196, 182, 162, 135 (base peak), 120, 107, 93, 79, 61, 41. Anal. Calcd for $C_{14}H_{22}NOF$: C, 70.26; H, 9.27; N, 5.85. Found: C, 70.26; H, 9.29; N, 5.94.

4.4.2. Reaction of 1-(1-adamantyl)-3-*tert*-butylaziridinone (5c) with aqueous hydrogenbromide. A solution of 9.3 mL (0.093 mol) of 48% (aq) HBr with 20 mL of distilled water was added to 1.21 g (0.0055 mol) of 1-(1-adamantyl)-3-*tert*-butylaziridinone (**5c**). The reaction mixture was stirred for 1 h at room temperature, then approximately 20 mL of liquid over a period of 1 h was distilled over into a receiving flask containing 0.736 g (0.0066 mol) of semicarbazide hydrochloride, 0.591 g (0.0072 mol) of sodium acetate, and 5 mL of distilled water, immersed in an ice/water bath. The receiving flask was then removed from the ice bath and stirred for an additional 45 min at room temperature. The reaction mixture was filtered on Büchner funnel and the solid washed with ice–cold water to afford 0.46 g (65.3%) of pure pivalaldehyde semicarbazone[38] with mp 188–191 °C (rep.[38] mp 191 °C). TLC (100% ethyl acetate) R_f=0.50. MS: *m/z* 143, 128, 111, 100, 86 (base peak), 84, 68, 57, 41.

The residue remaining in the distilling flask was washed with 15% Na_2CO_3 until the solution was basic. A solid precipitated and was collected on a Büchner funnel. It was dried and washed with 10 mL of ice cold ether and again filtered on a Büchner funnel to afford 0.69 g (95.0%) crude 1-adamantanamine. After recrystallization from acetone/methanol pure adamantanamine was obtained (mp 203–205 °C). TLC, IR, and MS were identical to an authentic sample (Aldrich) [TLC (100% ethanol) R_f=0.18. MS: *m/z* 151, 136, 108, 94 (base peak), 77, 57, 41].

4.4.3. Preparation of authentic pivalaldehyde semicarbazide. To a solution of pivalaldehyde (Lancaster, 0.86 g, 0.01 mol) in 35 mL of distilled water was added 1.22 g (0.011 mol) of semicarbazide hydrochloride and 0.984 g (0.012 mol) of sodium acetate. The solution was stirred for 1 h. The precipitate was collected on a Büchner funnel and washed with ice–cold water to afford 1.18 g (82.5%) of pure pivalaldehyde semicarbazone,[38] mp 191 °C (rep.[38] mp 191 °C). TLC (100% ethyl acetate) R_f=0.50. IR (CCl_4) ν: 3460, 3030, 2970, 1683 cm^{-1} (KBr) ν: 3460, 3300, 3180, 3040, 2940, 1690, 1645, 1625, 1600, 1500 cm^{-1}. MS: *m/z* 143, 128, 111, 100, 86 (base peak), 84, 68, 57, 41.

References and notes

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