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New Application of Pictet−Spengler Reaction Leading to the Synthesis of an Unusual Seven-Membered Heterocyclic Ring System†

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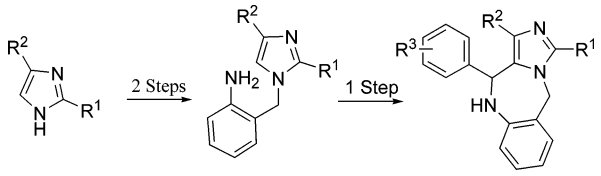

A novel strategy for the Pictet−Spengler reaction is reported. Our strategy involves reaction of arylamines, linked to the *N*-1 of disubstituted imidazoles, with aldehydes in the presence of *p*-TsOH. The iminium ion generated in situ undergoes C−C bond formation with the C-5 of the imidazoles to furnish triazabenzoazulenes as a novel heterosystem. Our strategy differs from conventional Pictet−Spengler reaction since the latter utilizes only aliphatic amines in which the amine functionality is linked to a C instead of N of the activated aromatic moiety.

For the last ∼100 years, the Pictet−Spengler reaction[1] has been widely used for C−C bond formation in ring systems referred to as tetrahydro-*β*-carbolines (THBCs) and tetrahydroisoquinolines (THIQs). However, despite being an attractive strategy, its application is limited to only the following three amine prototypes: Trp/tryptamine,[2] His/histamine,[3] and dopamine/tyramine.[2] A typical Pictet−Spengler reaction involves condensation of an aldehyde with amine (Trp or dopamine) to form an imine, which is often activated by Bronsted acids.[4] Final cyclization between a sufficiently reactive aromatic moiety and activated iminium ion results in a new carbon−carbon bond, forming a heterocyclic ring (Figure 1). In

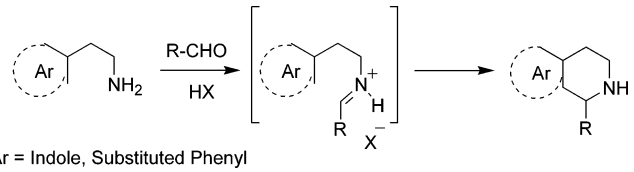

FIGURE 1. Typical acid-catalyzed Pictet−Spengler reaction.

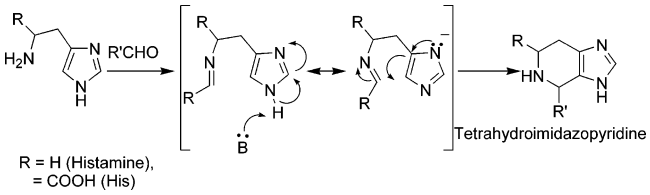

FIGURE 2. Typical base-catalyzed Pictet−Spengler reaction.

contrast, alkaline catalyst is used for Pictet−Spengler reaction involving His/histamine derived from imidazoles (Figure 2).[3d,e]

A careful survey of the literature revealed that Pictet−Spengler reaction has never been applied to arylamines linked to an activated aromatic nucleus. This prompted us to explore the use of arylamines linked to either *N* or *C* as a possible substrate for the Pictet−Spengler reaction.

The motivation stemmed from the fact that iminium ion derived from aromatic amine will facilitate C−C bond formation more than aliphatic amine since enhancement of the electrophilic nature of the iminium intermediate has been reported to be a driving force for cyclization.[5]

To begin with, we focused our attention on arylamines linked to the *N*-1 of imidazole and recently reported a modified strategy for Pictet−Spengler reaction on the solid phase leading to the synthesis of imidazoquinoxalines with three-point diversity.[6] This led us to believe that our modified strategy for the Pictet−Spengler reaction can be applied for the synthesis of a variety of heterosystems of medicinal significance. This is in con-

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trast to the conventional Pictet–Spengler reaction that furnishes either THBC/THIQ or tetrahydroimidazopyridines.

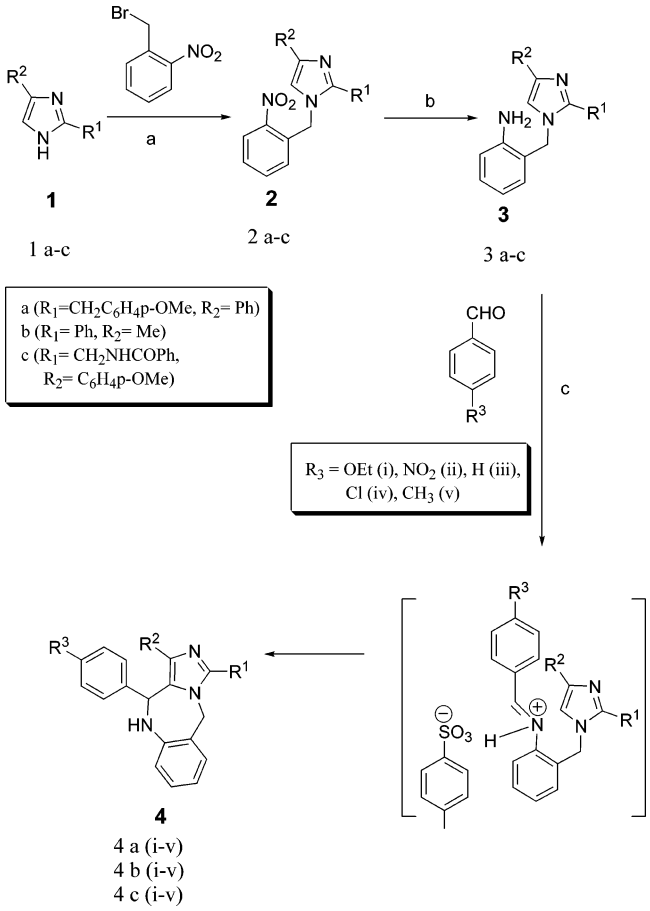
In this paper, we describe a new application of our strategy based on the Pictet–Spengler reaction that led to the synthesis of an unusual seven-membered heterocyclic skeleton: triazabenzoazulenes. Seven-membered azulenes are an important group of therapeutic agents with CNS activity.[7] To the best of our knowledge, this is the first report of this type of approach in the Pictet–Spengler reaction.

The synthetic strategy for triazabenzoazulene **4** with three-point diversity is depicted in Scheme 1. In the first instance, we decided to synthesize imidazoles **3** with aryl-NH_2 originating from *N*-1 of the ring. This was carried out by treating 2,4 disubstituted imidazoles **1** with *o*-nitrobenzyl bromide in the presence of NaH to get **2**. The resulting *N*-1 linked aryl nitro was then reduced to NH_2 functionality via catalytic hydrogenation to give **3**. An analogy between the imidazole derivative **3** (Scheme 1) and histamine (Figure 2) can be drawn from the fact that whereas in the former an aromatic amine functionality originates from *N*-1, in the latter, an aliphatic amine originates from the *C*-4. Further, in both the substrates, the *C*-5 that is involved in C–C bond formation is adjacent to the *N*-1 on one side and *C*-4 on the other side, which is considered to be a prerequisite for Pictet–Spengler reaction. Encouraged by these similarities, we then proceeded to study the utility of derivative **3** as an amine component for Pictet–Spengler reaction. In the first instance we treated imidazole derivative **3** with potassium hydroxide at reflux as described elsewhere for histamine.[3d] However, this failed in the formation of carbon–carbon bond between the imine and *C*-5 of imidazole. This led us to carry out the Pictet–Spengler reaction under a variety of reaction conditions such as acid-catalyzed and neutral conditions in order to optimize the cyclization via C–C bond formation.

Accordingly, we treated imidazole derivative **3** with *p*-ethoxybenzaldehyde in the presence of 5% TFA, 33% HBr, $Yb(OTf)_3$, acetic acid, and *p*-TsOH in the presence of methanol, toluene, and DCM as solvents. The best result was obtained when the Pictet–Spengler reaction was carried out in the presence of *p*TsOH in toluene at reflux for 18 to 20 h (Table 1). The completion of the reaction was monitored by TLC. In the initial stages of the reaction, the TLC exhibited a bright yellow spot due to the formation of Schiff base, which gradually disappeared and resulted in a new colorless spot probably due to the formation of **4**.

The solvent was then evaporated, and the residue was taken up in EtOAc and washed twice with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product so obtained was purified by silica gel column chromatography using 20–40% EtOAc–hexane to give the title compound **4**. The final compound was characterized using NMR and ESMS. However, for comparative studies, the Schiff base was also isolated and

SCHEME 1. Novel Strategy for Pictet–Spengler Reaction[a]



[a] Reaction conditions: (a) NaH, DMF, 30 min, rt; (b) Pd–C, H_2, 2 h; (c) *p*-TsOH, toluene, 125 °C, 18 h.

TABLE 1. Ratio of Imine and Triazabenzoazulene (4) Formed during Pictet–Spengler Reaction of 3 with *p*-Ethoxybenzaldehyde under Acidic and Neutral Conditions (Scheme 1)

conditions	imine[a] (%)	triazabenzoazulene[a] (%)
5% TFA, DCM, rt, 16 h	87	13
p-TsOH (0.1 equiv), MeOH, rt, 16 h	23	0
p-TsOH (0.1 equiv), toluene, reflux, 18 h	0	100
33% HBr in AcOH, EtOH, reflux, 2 h	41	0
$Yb(OTf)_3$, DCM, rt, 16 h	78	23
25% AcOH in DCM, rt, 12 h	80	0
MeOH, reflux, 12 h	33	0
toluene, reflux, o/n	83	10

[a] As evident by HPLC (C18 reversed-phase column; 250 × 4.6 mm; 10 μm).

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TABLE 2. ESMS of Compounds Based on 4

entry	product	R^1	R^2	R^3	% isolated yield	ESMS (M + H)
1	**4a(i)**	$CH_2C_6H_4$-*p*-OMe	C_6H_5	OC_2H_5	81	502.87
2	**4a(ii)**	$CH_2C_6H_4$-*p*-OMe	C_6H_5	NO_2	85	503.93
3	**4a(iii)**	$CH_2C_6H_4$-*p*-OMe	C_6H_5	H	82	458.87
4	**4a(iv)**	$CH_2C_6H_4$-*p*-OMe	C_6H_5	Cl	80	493.04
5	**4a(v)**	$CH_2C_6H_4$-*p*-OMe	C_6H_5	CH_3	87	472.87
6	**4b(i)**	C_6H_5	CH_3	OC_2H_5	76	395.93
7	**4b(ii)**	C_6H_5	CH_3	NO_2	80	397.13
8	**4b(iii)**	C_6H_5	CH_3	H	79	352.07
9	**4b(iv)**	C_6H_5	CH_3	Cl	75	386.13
10	**4b(v)**	C_6H_5	CH_3	CH_3	78	366.00
11	**4c(i)**	$CH_2NHCOC_6H_5$	C_6H_4-*p*-OMe	OC_2H_5	79	545.13
12	**4c(ii)**	$CH_2NHCO\ C_6H_5$	C_6H_4-*p*-OMe	NO_2	81	546.13
13	**4c(iii)**	$CH_2NHCO\ C_6H_5$	C_6H_4-*p*-OMe	H	88	501.07
14	**4c(iv)**	$CH_2NHCO\ C_6H_5$	C_6H_4-*p*-OMe	Cl	82	536.93
15	**4c(v)**	$CH_2NHCO\ C_6H_5$	C_6H_4-*p*-OMe	CH_3	77	515.00

characterized by ^{1}H NMR after quenching the reaction within 2 h. The ^{1}H NMR of the Schiff base exhibited characteristic signals due to the Schiff base proton at around 8.4 ppm and the *C*-5 proton of imidazole at around 7 ppm, whereas the cyclic product **4** exhibited disappearance of these two protons and emergence of a new signal at around 6.0 ppm due to the methine. The scope and limitation of our strategy was examined by utilizing three 2,4 disubstituted imidazoles[8] and five aldehydes. In all cases, the title compounds were obtained in excellent yields (75−88%) and were characterized using NMR, LC−MS, and HPLC. The structure and ESMS of 15 compounds based on **4** have been summarized in Table 2.

In summary we have for the first time demonstrated a new application of Pictet−Spengler reaction leading to the synthesis of an unusual seven membered ring 1) by changing the position of amine functionality in the imidazole ring and 2) by using aromatic amine instead of aliphatic amine. Further studies are in progress with Pictet−Spengler reaction on arylamines linked to the carbon of an activated aromatic nucleus.

Experimental Section

General Considerations. See the Supporting Information.

General Procedure for Synthesis of Imidazole 1a. Cesium carbonate (1.02 g, 3.125 mmol) was added to a solution of 4-methoxyphenylacetic acid (1.04 g, 6.25 mmol) in methanol (25 mL). The reaction mixture was stirred for 1 h, the solvent was evaporated, phenacyl bromide (1.24 g, 6.25 mmol) and dimethylformamide (20 mL) were added, and the mixture stirred overnight. The reaction mixture was evaporated to dryness under reduced pressure and xylene (30 mL) added to the residue. The cesium bromide salt was filtered, ammonium acetate (10 g) added to the filtrate, and the reaction mixture refluxed for 1.5 h using a Dean−Stark apparatus. After cooling, the reaction was diluted with ice−water and ethyl acetate (200 mL). The organic phase was washed with a saturated solution of sodium bicarbonate (100 mL) followed by brine (50 mL), dried over sodium sulfate, filtered, and evaporated to dryness under reduced pressure. Purification was carried out on a silica gel column to afford 0.40 g (24%) as a light cream powder: mp 148−150 °C.

2-(4-Methoxybenzyl)-4-phenyl-1*H*-imidazole (1a): 24%; pale yellow solid, mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.67 (d, 2H, J = 7.5 Hz, ArH), 7.36 (t, 2H, J = 7.5 Hz, ArH), 7.26−7.17 [m (o), 4H, ArH], 6.87 (d, 2H, J = 8.7 Hz, ArH), 4.09 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 157.4, 147.2, 133.7, 130.1, 129.1, 128.1, 125.5, 123.7, 113.4, 56.4, 33.0; IR (KBr) ν_{max} 3434.6 (br, NH), 1605.2. Mass (ES^+): *m/z* 265 (M^+ + 1). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.34; H, 6.08; N, 9.89.

General Procedure for *N*-Alkylation of Imidazoles 2. Imidazole **1a** (1.32 g, 5.0 mmol) was treated with NaH (0.13 g in 60% oil, 5.5 mmol) in DMF (10 mL) at rt for 15 min. Then *o*-nitrobenzyl bromide (1.14 g, 5.3 mmol) was added portionwise over a period of 5 min. The reaction was monitored by TLC, and after the completion of the reaction, the mixture was poured in ice-cold water (50 mL) and was extracted with EtOAc (2 × 25 mL). The EtOAc layer was washed with water (2 × 10 mL) and brine solution (1 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated to obtained yellow residue that after column chromatography on silica gel with hexane/EtOAc (20:80, v/v) as eluent afforded 1.70 g (85%) of **2a** as a yellow solid.

2-(4-Methoxybenzyl)-1-(2-nitrobenzyl)-4-phenyl-1*H*-imidazole (2a): 85%; yellow solid; mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.11 (dd, 1H, J = 3.9 Hz, ArH), 7.84 (d, 2H, J = 7.5 Hz, ArH), 7.48−7.40 [m (o), 4H, ArH], 7.28 (t, 1H, J = 7.2 Hz, ArH), 7.18 (s, 1H, ArH), 7.01 (d, 2H, J = 8.4 Hz, ArH), 6.66 (d, 2H, J = 8.7 Hz, ArH), 6.56 (dd, 1H, J = 3.3 Hz, ArH), 5.40 (s, 2H, CH_2), 4.05 (s, 2H, CH_2), 3.74 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 158.4, 148.1, 146.9, 140.9, 134.3, 134.0, 132.8, 130.1, 129.5, 128.8, 128.6, 128.3, 128.1, 127.0, 125.2, 124.9, 116.7, 114.3, 114.1, 55.3, 47.6, 33.3; IR (KBr) ν_{max} 1606, 1524, 1331 (NO_2); mass (ES^+) *m/z* 400 (M^+ + 1).

General Procedure for the Reduction of Nitro Group 3. A mixture of compound **2a** (1.50 g, 3.75 mmol) and Pd−C (100 mg) in methanol (10 mL) was subjected to hydrogenation in the Parr assembly at 35 psi at room temperature. The reaction was allowed to continue for 3 h. Thereafter, the catalyst was removed by vacuum filtering the reaction mixture through a Celite bed with methanol. The filtrate was evaporated to obtain an oily residue, which was taken up in EtOAc (2 × 20 mL) and washed with water (20 mL). The organic layers were evaporated in vacuo to obtain the crude oil, which was recrystallized in ethanol to obtain 1.10 g (80%) of **3a** as a white solid.

2-[2-(4-Methoxybenzyl)-4-phenylimidazol-1-ylmethyl]-phenylamine (3a): 80%; white solid; mp 177−179 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.73 (d, 2H, J = 7.5 Hz, ArH), 7.33 (t, 2H, J = 7.5 Hz, ArH), 7.25−7.12 [m (o), 4H, ArH], 6.49 (s, 1H, ArH), 6.84 [t (o), 3H, J = 8.7 Hz, ArH], 6.74 (t, 1H, J = 7.5 Hz, ArH), 6.64 (d, 1H, J = 8.1 Hz, ArH), 4.73 (s, 2H, CH_2), 4.13 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.28 (s, 2H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, 25 °C) δ 158.6, 147.5, 144.7, 140.3, 134.3, 129.7, 129.6, 129.0, 128.7, 126.7, 124.8, 119.7, 119.0, 116.5, 115.5, 114.3, 55.4, 47.3, 33.2; IR (KBr) ν_{max} 3461 (br, NH),1647, 1601; mass (ES^+) *m/z* 370 (M^+ + 1).

General Procedure for Pictet−Spengler Reaction 4. A mixture of imidazole-linked amine **3a** (0.1 g, 0.27 mmol),

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p-ethoxybenzaldehyde (0.40 g, 0.27 mmol), and *p*-tolylsulfonic acid (0.005 g, 0.02 mmol) was refluxed in toluene for 16 h. Toluene was evaporated in vacuo, and the residue so obtained was dissolved in ethyl acetate (25 mL). The organic layer was washed with water (2 × 10 mL) and brine solution (1 × 10 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 and evaporated to obtained yellow residue that after column chromatography on silica gel with hexane/EtOAc (40:60, v/v) as eluent afforded 0.11 g (81%) of **4a(i)** as white solid.

10-(4-Ethoxyphenyl)-3-(4-methoxybenzyl)-1-phenyl-9,10-dihydro-4*H*-2,3a,9-triazabenzo[*f*]azulene [4a(i)]: 81%; white solid; mp 190−192 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.66 (d, 2H, J = 7.2 Hz, ArH), 7.38 (t, 2H, J = 7.2 Hz, ArH), 7.30−7.23 [m (o), 3H, ArH], 7.04−6.99 [t (o), 3H, J = 8.4 Hz, ArH), 6.82 (d, 2H, J = 8.7 Hz, ArH), 6.75 (d, 2H, J = 8.4 Hz, ArH), 6.60 (d, 1H, J = 7.8 Hz, ArH), 6.44 (t, 1H, J = 7.5 Hz, ArH), 6.32 (d, 1H, J = 6.9 Hz, ArH), 5.95 (d, 1H, J = 6.6 Hz, CH), 4.86 (brd, 1H, J = 7.2 Hz, NH), 4.55 (d, 1H, J = 15.3 Hz, CH_2), 4.32 (d, 1H, J = 15.6 Hz, CH_2), 4.14 (q, 2H, J = 6.3 Hz, CH_2), 3.98 (q, 2H, J = 6.9 Hz, CH_2), 3.75 (s, 3H, OCH_3), 1.38 (t, 3H, J = 6.0 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 158.4, 158.2, 145.4, 145.2, 137.2, 134.8, 134.6, 129.9, 129.4, 129.2, 129.0, 128.6, 127.5, 127.1, 126.8, 118.1, 117.3, 114.9, 114.2, 63.5, 55.3, 51.5, 48.0, 33.0, 14.8; IR (KBr) ν_{max} 3431 (br, NH), 1597. Anal. Calcd for $C_{33}H_{31}N_3O_2$: C, 79.01; H, 6.23; N, 8.31. Found: C, 79.14; H, 6.32; N, 8.39.

3-(4-Methoxybenzyl)-10-(4-nitrophenyl)-1-phenyl-9,10-dihydro-4*H*-2,3a,9-triazabenzo[*f*]azulene [4a(ii)]: 85%; yellow solid; mp 165−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.15 (d, 2H, J = 8.7 Hz, ArH), 7.64 (d, 2H, J = 7.2 Hz, ArH), 7.53 (d, 2H, J = 8.7 Hz, ArH), 7.41 (t, 2H, J = 6.9 Hz, ArH), 7.32 (d, 1H, J = 7.2 Hz, ArH), 7.11−7.00 [m (o), 3H, ArH], 6.76 (d, 2H, J = 8.4 Hz, ArH), 6.66 (d, 1H, J = 7.8 Hz, ArH), 6.50 (t, 1H, J = 7.5 Hz, ArH), 6.31 (d, 1H, J = 6.6 Hz, ArH), 6.05 (s, 1H, CH), 4.86 (brd, 1H, NH), 4.39 (s, 2H, CH_2), 4.17 (q, 2H, J = 15.0 Hz, CH_2), 3.76 (s, 3H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 158.9, 150.8, 147.6, 146.5, 144.9, 138.0, 134.4, 130.4, 129.7, 129.5, 129.2, 127.9, 127.8, 127.6, 126.2, 124.5, 118.5, 118.2, 118.0, 114.6, 55.7, 52.4, 48.3, 33.1; IR (KBr) ν_{max} 3406 (br, NH) 1603, 1513, 1347 (NO_2). Anal. Calcd for $C_{31}H_{26}N_4O_3$: C, 74.09; H, 5.21; N, 11.15. Found: C, 73.92; H, 5.33; N, 11.15.

1-Methyl-3,10-diphenyl-9,10-dihydro-4*H*-2,3a,9-triazabenzo[*f*]azulene [4b(iii)]: 79%; white solid; mp 225−228 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.52 (d, 2H, J = 6.3 Hz, ArH), 7.47−7.24 [m (o), 8H, ArH], 7.14 (t, 1H, J = 8.1 Hz, ArH), 6.89 (d, 1H, J = 7.2 Hz, ArH), 6.79−6.66 [m (o), 2H, ArH], 4.83 (s, 1H, CH), 4.78 (s, 2H, CH_2), 2.28 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 146.2, 143.4, 134.1, 130.5, 130.1, 129.7, 129.4, 129.2, 129.1, 128.9, 128.1, 127.7, 126.6, 125.5, 119.8, 118.6, 118.4, 53.2, 48.9, 12.9; IR (KBr) ν_{max} 3474 (br, NH), 1597. Anal. Calcd for $C_{24}H_{21}N_3$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.12; H, 5.89; N, 11.99.

10-(4-Chlorophenyl)-1-methyl-3-phenyl-9,10-dihydro-4*H*-2,3a,9-triazabenzo[*f*]azulene [4b(iv)]: 75%; yellow solid; mp 205−207 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.52 (d, 2H, J = 6.3 Hz, ArH), 7.47−7.40 [m (o), 3H, ArH], 7.30 (s, 4H, ArH), 7.14(t, 1H, J = 7.5 Hz, ArH), 6.88 (d, 1H, J = 7.2 Hz, ArH), 6.74−6.67 [m (o), 2H, ArH], 5.75 (s, 1H, CH), 4.76 (s, 2H, CH_2), 2.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 146.1, 145.4, 141.5, 134.0, 133.2, 130.0, 129.6, 129.4, 129.0, 128.9, 128.7, 128.5, 127.7, 127.0, 120.0, 118.7, 118.3, 52.7, 48.5, 29.6; IR (KBr) ν_{max} 3397 (br, NH), 1597. Anal. Calcd for $C_{24}H_{20}ClN_3$: C, 74.70; H, 5.22; N, 10.89. Found: C, 74.76; H, 5.19; N, 10.72.

***N*-[1-(4-Methoxyphenyl)-10-(4-nitrophenyl)-9,10-dihydro-4*H*-2,3a,9-triazabenzo[*f*]azulen-3-ylmethyl]benzamide [4c-(ii)]:** 81%; yellow solid; mp 188−190 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 8.52 (brt, 1H, NH), 8.17 (d, 2H, J = 8.4 Hz, ArH), 7.86 (d, 2H, J = 7.5 Hz, ArH), 7.58 [d (o), 3H, J = 8.4 Hz, ArH], 7.48 (t, 1H, J = 6.9 Hz, ArH), 7.41 [d (overlapped with $CDCl_3$), 2H, J = 7.2 Hz, ArH], 7.02 (t, 1H, J = 7.5 Hz, ArH), 6.93 [t (o), 3H, J = 8.7 Hz, ArH], 6.74 (d, 1H, J = 8.1 Hz, ArH), 6.51 (d, 1H, J = 7.8 Hz, ArH), 6.41 (t, 1H, J = 7.2 Hz, ArH), 6.03 (d, 1H, J = 6.9 Hz, CH), 5.05−4.98 [m (o), 2H, CH_2], 4.66−4.52 [m (o), 2H, CH_2], 3.82 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 166.5, 158.5, 150.0, 146.5, 144.5, 142.9, 135.8, 133.1, 130.9, 129.6, 128.7, 128.0, 127.6, 126.9, 126.6, 125.9, 125.0, 123.4, 116.9, 116.4, 113.6, 54.6, 50.8, 47.0, 34.8; IR (KBr) ν_{max} 3404 (br, NH), 1647 (CONH), 1698, 1520, 1348 (NO_2). Anal. Calcd for $C_{32}H_{27}N_5O_4$: C, 70.45; H, 4.99; N, 12.84. Found: C, 70.44; H, 4.95; N, 12.85.

N-[1-(4-Methoxyphenyl)-10-*p*-tolyl-9,10-dihydro-4*H*-2,-3a,9-triazabenzo[*f*]azulen-3-ylmethyl]benzamide [4c(v)]: 77%; white solid; mp 146−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.74 (d, 2H, J = 7.2 Hz, ArH), 7.51 (d, 2H, J = 8.7 Hz, ArH), 7.46 (d, 1H, J = 7.2 Hz, ArH), 7.37 (t, 2H, J = 7.5 Hz, ArH), 7.25 [t (overlapped with $CDCl_3$), 2H, ArH], 7.15−7.02 [m (o), 4H, ArH, NH], 6.95 (d, 1H, J = 6.9 Hz, ArH), 6.90 (d, 2H, J = 6.9 Hz, ArH), 6.64 (d, 1H, J = 7.8 Hz, ArH), 6.50 (t, 1H, J = 7.5 Hz, ArH), 5.93 (d, 1H, J = 7.2 Hz, CH), 4.98−4.63 [m (o), 5H, 2xCH_2, NH], 3.81 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C) δ 167.4, 159.3, 145.5, 143.0, 139.9, 137.6, 137.5, 134.2, 131.9, 130.6, 130.1, 129.6, 129.0, 128.8, 127.9, 127.5, 127.2, 126.2, 118.3, 118.1, 117.7, 114.5, 55.7, 52.1, 48.1, 36.3, 21.3; IR (KBr) ν_{max} 3406 (br, NH), 1648 (CONH), 1605, 1490. Anal. Calcd for $C_{33}H_{30}N_4O_2$: C, 77.02; H, 5.88; N, 10.89. Found: C, 77.15; H, 5.82; N, 10.73.

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Supporting Information Available: ^{1}H NMR spectra of compounds **1a**, **4a(i)**−**(v)**, **4b(i)**−**(v)**, and **4c(i)**−**(v)**. ^{13}C NMR spectra of compounds **1a**, **4a(i)**−**(v)**, **4b(i)**−**(v)**, and **4c(i)**−**(v)**. 2-D HSQC NMR spectra of compounds **4a(i)** and **4c(ii)**. DEPT spectra of compounds **4a(i)**, **4c(ii)**, and **4c(iii)**. LC−MS profiles of compounds **4a(ii)**, **4b(iv)**, and **4c(iii)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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