

Full Paper

Epibatidine Alkaloid Chemistry: 5. Domino-Heck Reactions of Azabicyclic and Tricyclic Systems [†]

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[†] For the preceding paper in this series, see ref. [4]

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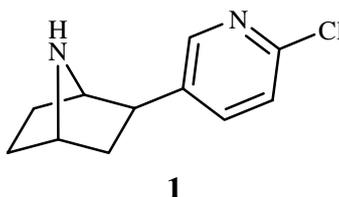
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Abstract: Palladium-catalyzed hydroarylations and additional domino reactions of azabicyclic and tricyclic norbornene derivatives were investigated and a series of new epibatidine analogues were synthesized.

Keywords: Epibatidine, Palladium, Hydroarylation, Domino Reactions, Heck Reactions, Alkynes, Heterocycles.

Introduction

Epibatidine (**1**), a novel class of amphibian alkaloid, was first isolated by Daly in trace amounts from the skin of the Ecuadorian poison frog *Epipedobates tricolor* [1]. The very high analgesic activity of **1** is a consequence of its high potency as an agonist towards nicotinic acetylcholine receptors (nAChRs) in the central and autonomic nervous systems [2]. The exciting biological properties and unique structure of **1**, combined with its scarcity in Nature (ca. 1 mg were obtained from some 750 frogs) have aroused the interest of synthetic chemists [3].

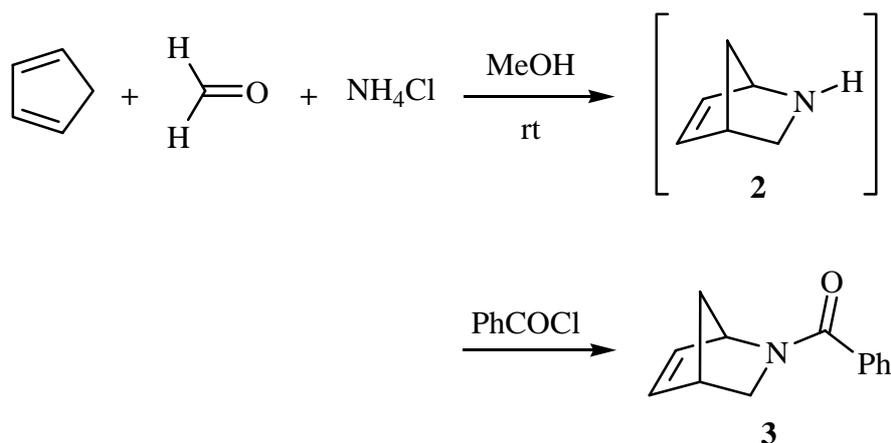


Despite the large number of syntheses of epibatidine published to date [4, 5], only a few analogues with modified pyridine rings have been prepared by reductive Heck reactions [6, 7]. In conjunction with this work we became interested in the possibility of synthesizing epibatidine analogues with modified bicyclic ring systems in a single synthetic operation via reductive Heck and additional domino-Heck reactions employing aryl(heteroaryl) iodides.

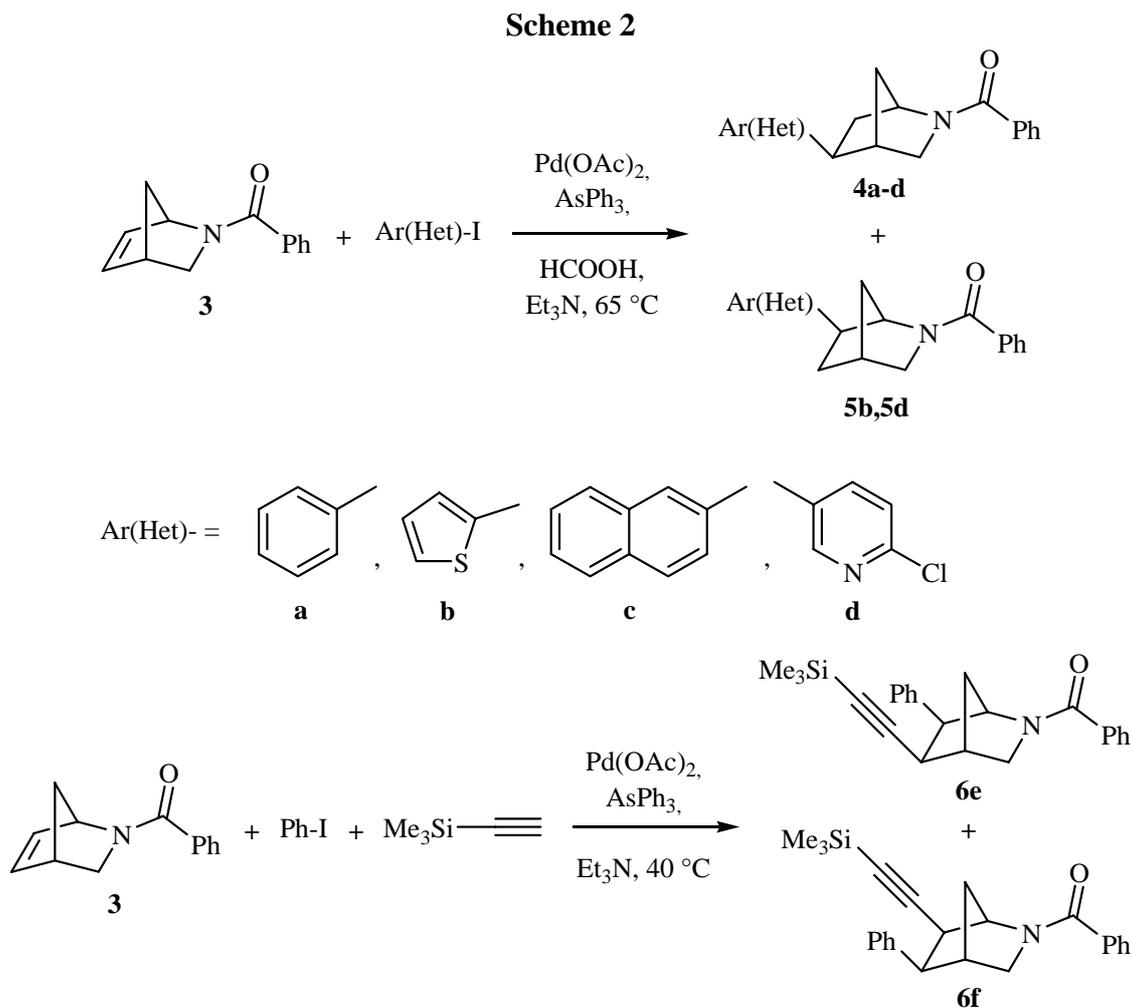
Results and Discussion

Our synthesis started with the Hetero-Diels-Alder reaction of cyclopentadiene and the iminium ion generated from formaldehyde and ammonium chloride [8]. The reaction occurred smoothly in aqueous methanol at room temperature to give the bicyclic amine **2**. Because of its unstable nature, this secondary amine was protected with benzoyl chloride to provide **3** in good yield (Scheme 1).

Scheme 1

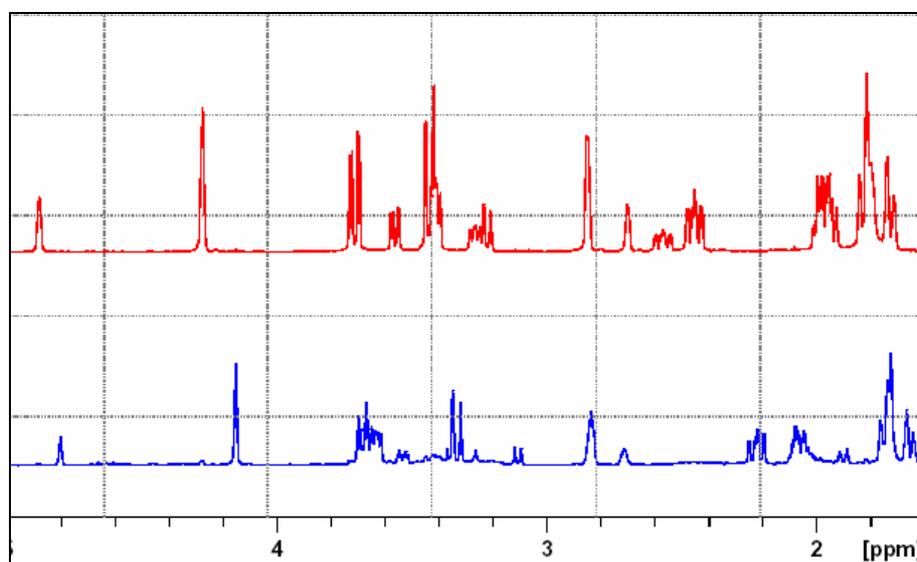


Due to the presence of rotamers, all the signals in the NMR spectra of **3** appear in pairs. Malpass and co-workers have previously prepared and protected compound **2** using both the benzyloxycarbonyl- (Cbz) and *t*-butoxycarbonyl (BOC) groups. They only worked with 2-chloro-5-iodopyridine under reductive Heck conditions using triphenylphosphine (PPh₃) as the ligand [6]. In our work excellent yields were obtained using triphenylarsine (AsPh₃) instead of PPh₃. Treatment of **3** with iodobenzene, 2-iodothiophene, 2-iodonaphthalene and 2-chloro-5-iodopyridine under reductive Heck conditions gave new compounds **4a-d** and **5b, 5d** as regioisomers after chromatographic separation. The reactions with iodobenzene and 2-iodonaphthalene gave only 5-*exo*- products. The use of trimethylsilylacetylene under domino-Heck conditions provided alkyne bicyclic systems **6e** and **6f** (Scheme 2). The reactivity of the bicyclic double bond in **3** is dependent on the nature of the *N*-protecting group.

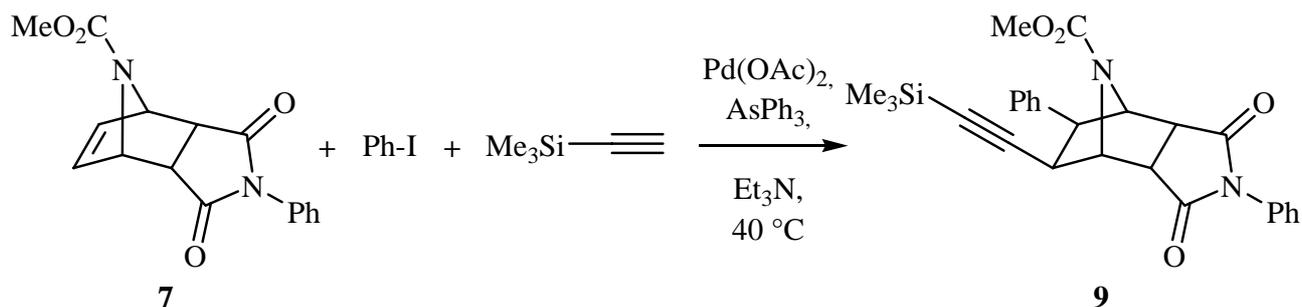


The regiochemistry of new compounds was inferred from their $^1\text{H-NMR}$ and HH-COSY spectra. For example, observation of the H_1 proton at 4.15 ppm in the $^1\text{H-NMR}$ spectra of **4b** (red spectrum in Figure 1), while it appeared at 4.04 ppm for **5b** (blue spectrum in Figure 1) was the first evidence for determining both *exo*-regioisomers. In the HH-COSY spectra of **4b**, an interaction between H_{6x} and H_1 was seen clearly, but the spectrum of **5b** did not show the same coupling due to the 6-*exo*- substituent.

Figure 1



Scheme 4. Cont.



Conclusions

The palladium-catalyzed hydroarylation of the easily accessible *N*-benzoylated 2-azabicyclo[2.2.1]heptene (**3**) in the presence of triphenylarsine as a ligand has been proven to be an excellent, versatile and high-yield approach to aryl- and heteroaryl analogues **4** and **5** of the bioactive alkaloid epibatidine (**1**); in case of aryl groups the reaction proceeds regioselectively. Reductive arylations of a diazatricyclic alkene **7**, synthesized by cycloaddition of a pyrrole carboxylic ester with *N*-phenylmaleimide, also succeeded under comparable reaction conditions. Domino-Heck sequential C-C couplings with aryl halides have been shown to be feasible in the presence of trimethylsilylacetylene. All Heck-type reactions proceed *exo*-selectively, leading to the same stereochemistry as found in **1**.

Experimental

General

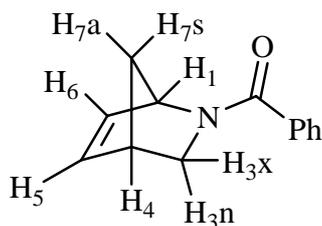
NMR spectra (CDCl_3 solvent) were recorded on Bruker Digital FT-NMR Avance 400 and Varian Inova 500 MHz NMR spectrometers, with TMS as internal reference. In the ^{13}C -NMR spectra quaternary, methylene and methyl carbons were identified using DEPT experiments. FTIR spectra (KBr) were recorded on a Perkin Elmer FT-IR spectrometer. GC-EIMS spectra were measured on a Varian SAT2100T/GC3900 spectrometer using ionisation by FAB. Reactions were performed under dry nitrogen. Melting points were measured on a Gallenkamp melting point apparatus. Silicagel 60 (Merck) was used for column chromatography separations. TLC was conducted on standard aluminium sheets pre-coated with a 0.2 mm layer of silica gel.

Heck Reactions – General procedure

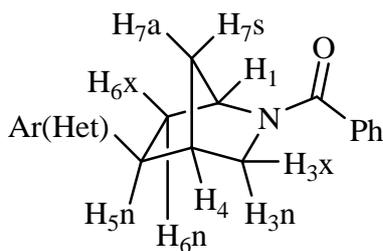
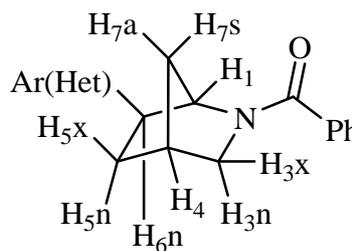
A solution of palladium(II) acetate [Pd(OAc)_2] (5.6 mg, 25 μmol) and AsPh_3 (33.7 mg, 11 μmol) in anhydrous DMF or DMSO (3 mL) was stirred under nitrogen at 65 $^\circ\text{C}$ for 15 min. Then, compounds **3** or **7** (1.0 mmol), Et_3N (488 μL , 3.5 mmol), the appropriate aryl(heteroaryl) iodide (1.5 mmol) and HCOOH (138 mg, 3.0 mmol) were added. The reaction mixture was stirred for 8–24 h. After cooling to r.t. EtOAc and brine added, the organic layer was separated, dried (MgSO_4), filtered and the solvent evaporated. The residue was purified by column chromatography.

Domino-Heck Reactions – General Procedure

$\text{Pd}(\text{OAc})_2$ (5.6 mg, 25 μmol) and the arsine ligand (55 μmol) were dissolved in dry DMF (3 mL) and the solution was stirred at 40 °C for 15 min. Then, **3** or **7** (1.0 mmol), the aryl compound (1.5 mmol), triethylamine (488 μL , 3.50 mmol) and trimethylsilylacetylene (3.00 mmol) were added rapidly in one portion. The mixture was heated at the same temperature for 24 h. After cooling down to r.t. brine (50 mL) was added, the reaction mixture was extracted with ethyl acetate and dried over MgSO_4 . The solvent was evaporated and the residue purified by column chromatography.

N-Benzoyl-2-azabicyclo[2.2.1]hept-5-ene (**3**)

Freshly distilled cyclopentadiene (4 mL, 50 mmol) was added to a solution of NH_4Cl (1.325 g, 25 mmol), 36% aqueous formaldehyde (2.6 mL, 35 mmol) and MeOH (5 mL). The reaction mixture was stirred overnight at r.t. The resulting light yellow solution was diluted with an equal volume of water and washed with diethyl ether (2x15 mL). To a mixture of this extract and 10% NaOH (5 mL) benzoyl chloride (2.10 g, 10 mmol) was added over 10 min at r.t. and the mixture was allowed to stir for 2 h. The organic layer was separated, dried over Na_2SO_4 , filtered and the solvent removed under reduced pressure to give a yellow oil that was separated by column chromatography (1:1 ethyl acetate-*n*-hexane) to give **3** in 83% yield; colorless crystals; R_f : 0.57; mp 49-51 °C; IR: 3060, 1622, 1575, 1495, 1426, 1176, 710, 659 cm^{-1} ; $^1\text{H-NMR}$ (rotamer ratio= 1:0.6) δ : 1.56-1.62 (dd, $J=8.0$, 6.5 Hz, 4H, H_{7a} and H_{7s}), [2.54-2.56 (dd, $J=1.5$, 1.5 Hz, minor rotamer) and 2.90-2.92 (dd, $J=1.5$, 1.5 Hz, major rotamer), 2H, H_{3n}], [3.14 (bs, minor rotamer) and 3.24 (bs, major rotamer), 2H, H_4], 3.49-3.55 (m, major and minor rotamers, 2H, H_{3x}), [4.46 (bs, major rotamer) and 5.14 (bs, minor rotamer), 2H, H_1], [6.18-6.20 (dd, $J=2.0$, 2.0 Hz, minor rotamer) and 6.20-6.22 (dd, $J=2.0$, 2.0 Hz, major rotamer, 2H, H_6)], [6.34-6.36 (dd, $J=2.0$, 2.0 Hz, major rotamer) and 6.48-6.50 (dd, $J=2.0$, 2.0 Hz, minor rotamer), 2H, H_5], 7.30-7.45 (m, 10H, aromatic protons); $^{13}\text{C-NMR}$ δ : 42.8, 45.9, 49.2, 64.0, 127.3, 128.5, 128.6, 133.4, 137.3, 138.5, 171.3 (major rotamer); 44.0, 47.6, 49.8, 60.5, 127.6, 128.4, 130.3, 133.2, 135.9, 136.6, 169.5 (minor rotamer); MS: m/z 199 [M^+], $\text{C}_{13}\text{H}_{13}\text{NO}$.

**4a-d****5a, 5d**

N-Benzoyl-5-*exo*-phenyl-2-azabicyclo[2.2.1]heptane (**4a**).

Purified by column chromatography (1:1 ethyl acetate-*n*-hexane) as colorless crystals in 91% yield; R_f : 0.42; mp 81-83 °C; IR: 3030, 1622, 1575, 1494, 1423, 1195, 710, 653 cm^{-1} ; $^1\text{H-NMR}$ (rotamer ratio=1:0.5) δ : 1.51-1.70 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), [1.76-1.86 (m, major rotamer) and 1.92-2.20 (m, minor rotamer), 2H, H_{6x}], [2.26-2.32 (ddt, $J=2.0, 2.5$ Hz, major rotamer) and 2.38-2.45 (ddt, $J=2.5, 2.5$ Hz, minor rotamer), 2H, H_{6n}], [2.60 (bs, minor rotamer) and 2.74 (bs, major rotamer), 2H, H_4], [2.90-2.96 (m, minor rotamer) and 3.06-3.14 (m, major rotamer), 2H, H_{5n}], [3.24-3.28 (m, minor rotamer) and 3.32-3.36 (m, major rotamer), 2H, H_{3n}], [3.40-3.48 (m, minor rotamer) and 3.54-3.64 (m, major rotamer), 2H, H_{3x}], [4.08 (bs, major rotamer) and 4.74 (bs, minor rotamer), 2H, H_1], [7.08-7.27 (m, major and minor rotamers), 10H, aromatic protons], [7.30-7.51 (m, major and minor rotamers), 10H, aromatic protons]; $^{13}\text{C-NMR}$ δ : 35.2, 36.4, 40.6, 42.6, 53.5, 57.4, 126.6, 126.9, 127.2, 127.4, 128.6, 128.8, 130.1, 137.1, 144.9, 169.2 (major rotamer); 35.0, 35.7, 39.0, 44.1, 52.4, 56.9, 126.4, 127.0, 127.1, 127.4, 128.5, 128.8, 130.1, 135.4, 142.5, 169.6 (minor rotamer); MS: m/z 277 [M^+], $\text{C}_{19}\text{H}_{19}\text{NO}$.

N-Benzoyl-5-*exo*-(2-thienyl)-2-azabicyclo[2.2.1]heptane (**4b**).

Separated by column chromatography (4:1 ethyl acetate-*n*-hexane) as a yellow oil, yield 57%; R_f : 0.67; IR: 3028, 1624, 1575, 1424, 1197, 798, 700 cm^{-1} ; $^1\text{H-NMR}$ (rotamer ratio=1:0.4) δ : 1.58-1.74 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), 1.80-1.89 (m, major and minor rotamers, 2H, H_{6x}), [2.30-2.36 (ddt, $J=2.5, 2.5$ Hz, major rotamer) and 2.42-2.48 (ddt, $J=2.0, 2.0$ Hz, minor rotamer), 2H, H_{6n}], [2.58 (bs, minor rotamer) and 2.72 (bs, major rotamer), 2H, H_4], 3.13-3.19 (m, major and minor rotamers, 2H, H_{5n}), 3.23-3.34 (m, major and minor rotamers, 2H, H_{3n}), [3.41-3.46 (dd, $J=3.5, 3.0$ Hz minor rotamer) and 3.59-3.62 (dd, $J=3.5, 3.5$ Hz, major rotamer), 2H, H_{3x}], [4.15 (bs, major rotamer) and 4.74 (bs, minor rotamer), 2H, H_1], 6.72-6.75 (m, major and minor rotamers, 2H, thienyl protons), 6.83-6.88 (m, major and minor rotamers, 2H, thienyl protons), 7.04-7.08 (m, major and minor rotamers, 2H, thienyl protons), 7.30-7.46 (m, major and minor rotamers, 10H, aromatic protons); $^{13}\text{C-NMR}$ δ : 36.2, 41.3, 41.8, 44.4, 52.5, 59.8, 123.1, 123.3, 126.8, 127.1, 128.4, 130.0, 136.6, 149.3, 169.0 (major rotamer); 34.8, 40.3, 41.1, 45.7, 54.5, 56.7, 123.1, 123.3, 126.8, 127.2, 128.3, 130.1, 136.5, 149.5, 169.7 (minor rotamer); MS: m/z 283 [M^+], $\text{C}_{17}\text{H}_{17}\text{NOS}$.

N-Benzoyl-5-*exo*-(2-naphthyl)-2-azabicyclo[2.2.1]heptane (**4c**).

Separated by column chromatography (1:1 ethyl acetate-*n*-hexane) as white crystals, yield 96%; R_f : 0.42; mp 56-58 °C; IR: 3034, 1625, 1574, 1508, 1260, 779, 701 cm^{-1} ; $^1\text{H-NMR}$ (rotamer ratio=1:0.8) δ : 1.71-1.92 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), [1.93-2.01 (m, major rotamer) and 2.03-2.12 (m, minor rotamer), 2H, H_{6x}], [2.29-2.35 (dddd, $J=1.5, 2.0, 2.0, 3.0$ Hz, major rotamer) and 2.57-2.64 (dddd, $J=2.0, 2.5, 2.5, 3.0$ Hz, minor rotamer), 2H, H_{6n}], [2.83 (bs, minor rotamer) and 2.90 (bs, major rotamer), 2H, H_4], [3.18-3.22 (d, $J=9.5$ Hz, minor rotamer) and 3.34-3.38 (d, $J=9.0$ Hz, major rotamer), 2H, H_{5n}], [3.48-3.52 (dd, $J=1.0, 1.0$ Hz, minor rotamer) and 3.56-3.60 (dd, $J=1.0, 1.5$ Hz major rotamer) 2H, H_{3n}], [3.65-3.72 (m, minor rotamer) and 3.76-3.82 (m, major rotamer), 2H, H_{3x}],

[4.55 (bs, major rotamer) and 5.01 (bs, minor rotamer), 2H, H₁], 7.11-7.20 (d, $J=7.0$ Hz, major rotamer, 1H, aromatic proton), 7.28-7.47 (m, major and minor rotamers, 13H, aromatic protons), 7.48-7.62 (m, major and minor rotamers, 4H aromatic protons), 7.66-7.70 (d, $J=9.5$ Hz, minor rotamer, 1H, aromatic proton), 7.71-7.74 (d, $J=8.0$ Hz, major rotamer, 1H, aromatic proton), 7.80-7.83 (d, $J=8.5$ Hz, minor rotamer, 1H, aromatic proton), 7.84-7.88 (d, $J=8.0$ Hz, major rotamer, 1H, aromatic proton), 7.98-8.02 (d, $J=7.5$ Hz, minor rotamer, 1H, aromatic proton), 8.04-8.08 (d, $J=9.0$ Hz, major rotamer, 1H, aromatic proton); ¹³C-NMR δ : 35.1, 37.0, 39.4, 41.4, 53.5, 60.5, 121.4, 124.0, 125.5, 125.9, 126.3, 127.3, 127.5, 128.7, 129.2, 130.2, 131.8, 134.2, 137.0, 140.6, 169.2 (major rotamer); 34.7, 37.0, 39.7, 41.3, 52.9, 60.9, 122.1, 123.7, 125.3, 125.9, 126.3, 127.2, 127.4, 128.6, 129.0, 130.2, 131.7, 134.4, 136.9, 141.0, 169.0 (minor rotamer); MS: m/z 327 [M⁺], C₂₃H₂₁NO.

N-Benzoyl-5-exo-(2-chloro-5-pyridinyl)-2-azabicyclo[2.2.1]heptane (4d).

Separated by column chromatography (1:1 ethyl acetate-*n*-hexane) as a colorless oil, yield 54%; R_f: 0.45; IR: 3065, 1627, 1574, 1508, 1260, 780, 714 cm⁻¹; ¹H-NMR (rotamer ratio=1:0.6) δ : 1.52-1.70 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), [1.78-2.20 (m, major and minor rotamers), 2H, H_{6x}], [2.28-2.32 (dddd, $J=2.0, 2.0, 2.5, 2.5$ Hz, major rotamer) and 2.38-2.44 (dddd, $J=2.0, 2.0, 2.5, 2.5$ Hz, minor rotamer), 2H, H_{6n}], [2.62 (bs, minor rotamer) and 2.74 (bs, major rotamer), 2H, H₄], [2.90-3.00 (m, minor rotamer) and 3.06-3.15 (m, major rotamer), 2H, H_{5n}], [3.22-3.28 (m, minor rotamer) and 3.33-3.38 (m, major rotamer) 2H, H_{3n}], [3.43-3.48 (m, minor rotamer) and 3.52-3.62 (m, major rotamer), 2H, H_{3x}], [4.14 (bs, major rotamer) and 4.78 (bs, minor rotamer), 2H, H₁], 7.26-7.28 (d, $J=8.0$ Hz, major and minor rotamers, 2H, aromatic protons), 7.30-7.47 (m, major and minor rotamers, 10H, aromatic protons), 7.47-7.49 (dd, $J=8.0, 3.0$ Hz, 2H, major and minor rotamers, aromatic protons), 8.22-8.24 (d, $J=3.0$ Hz, 2H, major and minor rotamers, aromatic protons); ¹³C-NMR δ : 35.1, 36.4, 40.5, 42.7, 53.4, 57.5, 126.6, 126.9, 127.1, 128.5, 128.7, 130.0, 136.7, 139.2, 148.4, 169.1 (major rotamer), 35.0, 36.2, 40.8, 42.9, 54.0, 57.9, 127.0, 127.2, 128.9, 129.0, 130.5, 137.0, 139.8, 148.7, 170.2 (minor rotamer); MS: m/z 312 [M⁺], C₁₈H₁₇ClN₂O.

N-Benzoyl-6-exo-(2-thienyl)-2-azabicyclo[2.2.1]heptane (5b).

Separated by column chromatography (4:1 ethyl acetate-*n*-hexane) as yellow crystals, yield 40%; R_f: 0.60; mp 98-100 °C, IR: 3025, 1613, 1571, 1430, 1074, 789, 716 cm⁻¹; ¹H-NMR (rotamer ratio=1:0.3) δ : 1.52-1.66 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), 1.92-1.98 (m, major and minor rotamers, 2H, H_{5x}), 2.08-2.14 (m, major and minor rotamers, 2H, H_{5n}), [2.60 (bs, minor rotamer) and 2.72 (bs, major rotamer), 2H, H₄], [3.08-3.11 (dd, $J=1.0, 1.0$ Hz, minor rotamer) and 3.20-3.23 (dd, $J=1.5, 1.5$ Hz major rotamer), 2H, H_{3n}], [3.40-3.43 (tt, minor rotamer) and 3.49-3.52 (m, major rotamer), 2H, H_{3x}], 3.54-3.60 (m, major and minor rotamers, 2H, H_{6n}), [4.04 (bs, major rotamer) and 4.70 (bs, minor rotamer), 2H, H₁], 6.82-6.90 (dd, $J=1.0, 1.0$ Hz, major and minor rotamers, 2H, thienyl protons), 7.04-7.10 (dd, $J=1.0, 1.0$ Hz, major and minor rotamers, 4H, thienyl protons), 7.28-7.52 (m, major and minor rotamers, 10H, aromatic protons); ¹³C-NMR δ : 35.7, 37.1, 39.2, 45.0, 52.1, 65.8, 123.4, 123.6, 127.0, 127.1, 128.4, 130.2, 136.2, 146.6, 168.9 (major rotamer), 36.2, 37.5, 39.5, 43.1,

56.9, 62.2, 123.3, 123.8, 126.9, 127.3, 128.3, 130.2, 136.6, 147.6, 169.5 (minor rotamer); MS: m/z 283 [M⁺], C₁₇H₁₇NOS.

N-Benzoyl-6-*exo*-(2-chloro-5-pyridinyl)-2-azabicyclo[2.2.1]heptane (**5d**).

Separated by column chromatography (1:1 ethyl acetate-*n*-hexane) as a colorless oil, yield 40%; R_f: 0.39; IR: 3065, 1625, 1575, 1510, 1260, 781, 712 cm⁻¹; ¹H-NMR (rotamer ratio=1:0.55) δ: 1.52-1.68 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), [1.92-2.00 (m, major rotamer and minor rotamers), 2H, H_{5x}], [2.02-2.12 (m, major rotamer and minor rotamers), 2H, H_{5n}], [2.60 (bs, minor rotamer) and 2.74 (bs, major rotamer), 2H, H₄], [3.08-3.13 (dd, *J*= 1.0, 1.0 Hz, minor rotamer) and 3.19-3.24 (dd, *J*=1.5, 1.5 Hz, major rotamer), 2H, H_{3n}], [3.40-3.45 (tt, minor rotamer) and 3.48-3.52 (tt, major rotamer) 2H, H_{3x}], 3.54-3.58 (m, major rotamer and minor rotamers), 2H, H_{6n}], [4.16 (bs, major rotamer) and 4.72 (bs, minor rotamer), 2H, H₁], 7.20-7.40 (m, major and minor rotamers, 12H, aromatic protons), 7.41-7.50 (dd, *J*=8.5, 2.5 Hz, major and minor rotamers, 2H, aromatic protons), 8.16-8.18 (d, *J*=2.5 Hz, major and minor rotamers, 2H, aromatic protons); ¹³C-NMR δ: 35.2, 36.5, 37.2, 45.1, 52.0, 62.0, 126.8, 127.8, 128.1, 128.6, 130.1, 136.9, 145.3, 149.4, 169.7 (major rotamer), 35.4, 36.8, 37.8, 45.7, 52.3, 61.8, 127.0, 128.0, 128.2, 128.9, 131.0, 137.4, 145.6, 149.8, 170.0 (minor rotamer); MS: m/z 312 [M⁺], C₁₈H₁₇ClN₂O.

N-Benzoyl-5-*exo*-(trimethylsilylethynyl)-6-*exo*-phenyl-2-azabicyclo[2.2.1]heptane (**6e**).

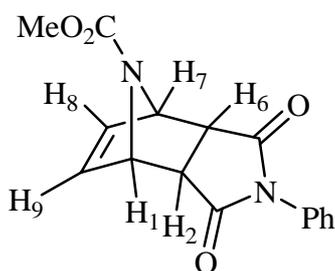
Separated by column chromatography (2:3 ethyl acetate-*n*-hexane) as yellow crystals, yield 60%; R_f: 0.38; mp 113-115 °C; IR: 3025, 2177, 1629, 1574, 1427, 1085, 840, 696 cm⁻¹; ¹H-NMR (rotamer ratio=1:0.4) δ: -0.154 (s, major rotamer, 9H, Si(CH₃)₃), -0.145 (s, minor rotamer, 9H, Si(CH₃)₃), 1.81-1.89 (m, major and minor rotamers, 4H, H_{7a} and H_{7s}), [2.19-2.22 (d, *J*=10.4 Hz, major rotamer) and 2.29-2.31 (d, *J*=10.8 Hz, minor rotamer), 2H, H_{6n}], [2.78 (bs, minor rotamer) and 2.89 (bs, major rotamer), 2H, H₄], [3.11-3.13 (m, minor rotamer) and 3.24-3.31 (m, major rotamer), 2H, H_{5n}], 3.46-3.50 (dd, *J*=4.0, 3.6 Hz, minor rotamer, 1H, H_{3n}), [3.69-3.72 (dd, *J*=4.0, 4.0 Hz, major rotamer) and 3.51-3.53 (d, *J*=9.6, minor rotamer), 2H, H_{3x}], 3.55-3.57 (d, *J*=9.2 Hz, major rotamer, 1H, H_{3n}), [4.40 (bs, major rotamer) and 5.05 (bs, minor rotamer), 2H, H₁], 7.06-7.28 (m, major and minor rotamers, 10H, aromatic protons), 7.29-7.54 (m, major and minor rotamers, 10H, aromatic protons); ¹³C-NMR δ: -0.42, 36.4, 40.9, 43.6, 50.9, 53.5, 62.6, 89.6, 106.0, 126.4, 127.1, 127.9, 128.0, 128.4, 130.0, 136.0, 139.0, 168.3 (major rotamer), -0.51, 34.9, 40.6, 44.9, 51.9, 54.5, 58.8, 89.6, 106.3, 126.2, 127.2, 127.7, 128.3, 128.4, 130.1, 136.1, 139.8, 169.2 (minor rotamer); MS: m/z 373[M⁺], C₂₄H₂₇SiNO.

N-Benzoyl-6-*exo*-(trimethylsilylethynyl)-*exo*-5-phenyl-2-azabicyclo[2.2.1]heptane (**6f**).

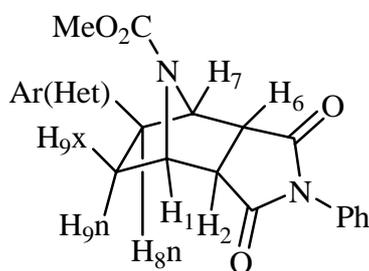
Separated by column chromatography (2:3 ethyl acetate-*n*-hexane) as yellow crystals, yield 35%; R_f: 0.43; mp 128-130 °C; IR: 3026, 2171, 1626, 1573, 1418, 1072, 835, 695 cm⁻¹; ¹H-NMR (rotamer ratio=1:0.4) δ: -0.199 (s, major rotamer, 9H, Si(CH₃)₃), -0.147 (s, minor rotamer, 9H, Si(CH₃)₃), [1.84-1.86 (m, major rotamer) and 1.90-1.93 (m, minor rotamer), 4H, H_{7a} and H_{7s}], [2.26-2.29 (d, *J*=10.0 Hz, major rotamer) and 2.37-2.39 (d, *J*=10.4 Hz, minor rotamer), 2H, H_{6n}], [2.83 (bs, minor rotamer) and

2.98 (bs, major rotamer), 2H, H₄], 3.13-3.16 (m, major and minor rotamers, 2H, H_{5n}), 3.37-3.41 (m, major and minor rotamers, 2H, H_{3n}), [3.56-3.59 (dd, $J=3.6, 3.2$ Hz, minor rotamer) and 3.64-3.68 (dd, $J=3.6, 3.2$ Hz, major rotamer), 2H, H_{3x}], [4.24 (bs, major rotamer) and 4.78 (bs, minor rotamer), 2H, H₁], 7.15-7.25 (m, major and minor rotamers, 5H, aromatic protons), 7.26-7.31 (m, major and minor rotamers, 4H, aromatics), 7.40-7.48 (m, major and minor rotamers, 5H, aromatic protons), 7.52-7.56 (m, major and minor rotamer, 6H, aromatic protons); ¹³C-NMR δ : -0.51, 36.9, 40.2, 44.7, 50.2, 54.0, 64.4, 91.2, 103.5, 126.3, 127.1, 127.9, 128.0, 128.5, 130.1, 136.1, 140.9, 169.3 (major rotamer), -0.43, 34.8, 41.8, 43.0, 49.6, 57.8, 61.1, 90.6, 104.1, 126.2, 127.2, 127.8, 128.0, 128.3, 130.2, 136.1, 141.1, 169.8 (minor rotamer); MS: m/z 373 [M⁺], C₂₄H₂₇SiNO.

endo-Methyl 3,5-dioxo-4-phenyl-4,10-diazatricyclo[5.2.1.0^{2,6}]dec-8-ene-10-carboxylate (**7**).



IR: 3065, 1774, 1713, 1697 cm⁻¹; ¹H-NMR δ : 2.96 (s, 2H, H₂ and H₆), 3.62 (s, 3H, -OCH₃), 5.21 (s, 2H, H₁ and H₇), 6.58 (s, 2H, H₈ and H₉), 7.24-7.48 (m, 5H, aromatic protons); ¹³C-NMR δ : 53.1, 63.5, 126.3, 128.8, 129.1, 131.5, 156.0, 174.5, 175.1; MS: m/z 298 [M⁺], C₁₆H₁₄N₂O₄.



endo-Methyl 3,5-dioxo-4,8_{exo}-diphenyl-4,10-diazatricyclo[5.2.1.0^{2,6}]decane-10-carboxylate (**8a**)

Separated by column chromatography (2:1 ethyl acetate-*n*-hexane) as colorless crystals, yield 55%; R_f: 0.49; mp 220-222 °C; IR: 3061, 1777, 1713, 1698 cm⁻¹; ¹H-NMR δ : 2.12-2.23 (m, 2H, H_{9x} and H_{9n}), 3.09-3.26 (m, 2H, H₂ and H₆), 3.46 (s, 3H, -OCH₃), 3.57 (s, 1H, H_{8n}), 4.75 (bs, 1H, H₁), 5.06 (bs, 1H, H₇), 7.21-7.33 (m, 5H, aromatic protons); 7.36-7.48 (m, 5H, aromatic protons); ¹³C-NMR δ : 37.9, 47.7, 49.3, 50.7, 52.9, 60.6, 65.3, 126.3, 127.2, 128.8, 129.3, 131.9, 142.9, 155.3, 175.2, 175.4; MS: m/z 375 [M⁺], C₂₂H₂₀N₂O₄.

endo-Methyl 8-*exo*-(4-chlorophenyl)-3,5-dioxo-4-phenyl-4,10-diazatricyclo[5.2.1.0^{2,6}]decane-10-carboxylate (**8b**).

Separated by column chromatography (1:1 ethyl acetate-*n*-hexane) as colorless crystals, yield 72%; R_f: 0.40; mp 182-84 °C; IR: 3058, 1776, 1716, 1695 cm⁻¹; ¹H-NMR (δ): 2.07-2.21 (m, 2H, H_{9x} and H_{9n}),

3.07-3.24 (m, 2H, H₂ and H₆), 3.47 (s, 3H, -OCH₃), 3.57 (s, 1H, H_{8n}), 4.70 (bs, 1H, H₁), 5.06 (bs, 1H, H₇), 7.23-7.29 (m, 5H, aromatic protons), 7.36-7.41 (m, 2H, aromatic protons), 7.46-7.48 (m, 2H, aromatic protons); ¹³C-NMR δ: 37.8, 46.8, 49.0, 50.3, 52.9, 59.2, 65.0, 126.4, 128.3, 128.6, 128.8, 129.1, 131.4, 132.9, 141.2, 155.2, 174.9, 175.0; MS: m/z 410 [M⁺], C₂₂H₁₉ClN₂O₄.

endo-Methyl 3,5-dioxo-4-phenyl-8-exo-(2-thienyl)-4,10-diazatricyclo[5.2.1.0^{2,6}]decane-10-carboxylate (8c).

Separated by column chromatography (1:1 ethyl acetate-*n*-hexane) as colorless crystals, yield 58%; R_f: 0.43; mp 224-226 °C; IR: 3112, 3064, 1778, 1713, 1691 cm⁻¹; ¹H-NMR δ: 2.22-2.24 (m, 2H, H_{9x} and H_{9n}), 3.10-3.12 (dd, *J*=7.5, 4.0 Hz, 1H, H₆), 3.21-3.24 (d, *J*=9.0 Hz, 1H, H₂), 3.45 (s, 3H, -OCH₃), 3.57 (s, 1H, H_{8n}), 4.75 (bs, 1H, H₁), 5.04 (bs, 1H, H₇), 6.92-6.94 (dd, *J*=4.5, 4.5 Hz, 2H, thienyl protons), 7.24-7.26 (m, 1H, thienyl proton), 7.37-7.49 (m, 5H, aromatic protons); ¹³C-NMR δ: 38.7, 48.7, 49.6, 52.7, 58.9, 65.8, 124.0, 124.4, 126.0, 126.4, 126.6, 128.8, 129.1, 131.4, 146.2, 155.4, 174.9, 175.0; MS: m/z 382 [M⁺], C₂₀H₁₈N₂O₄S.

endo-Methyl 3,5-dioxo-9-exo-(trimethylsilylethynyl)-4,8-exo-diphenyl-4,10-diazatricyclo-[5.2.1.0^{2,6}]-decane-10-carboxylate (9).

Separated by column chromatography (1:1 ethyl acetate-*n*-hexane) as yellow crystals, yield 42%; R_f: 0.52; mp 196-198 °C; IR: 3033, 1781, 1717, 1693 cm⁻¹; ¹H-NMR δ: 0.0 (s, 9H, Si(CH₃)₃), 3.31-3.48 (m, 4H, H_{9n}, H_{8n}, H₂ and H₆), 3.78 (s, 3H, -OCH₃), 5.08 (bs, 1H, H₁), 5.31 (bs, 1H, H₇), 7.36-7.45 (m, 5H, aromatic protons), 7.47-7.64 (m, 5H, aromatic protons); ¹³C-NMR δ: 0.52, 42.9, 49.0, 49.9, 51.6, 53.0, 63.1, 64.5, 91.6, 102.7, 125.9, 126.0, 127.0, 128.0, 128.3, 128.8, 129.2, 134.2, 139.0, 154.4, 174.3, 174.5; MS: m/z 472 [M⁺], C₂₇H₂₈SiN₂O₄.

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Sample Availability: Samples of the compounds are available from the authors.

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