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PALLADIUM-CATALYZED HETEROARYLAMINATION OF ETHYL 2-CHLORO-1-AZAAZULENE-3-CARBOXYLATE AND ANNULATION OF HETEROARYLAMINO-1-AZAAZULENES[†]

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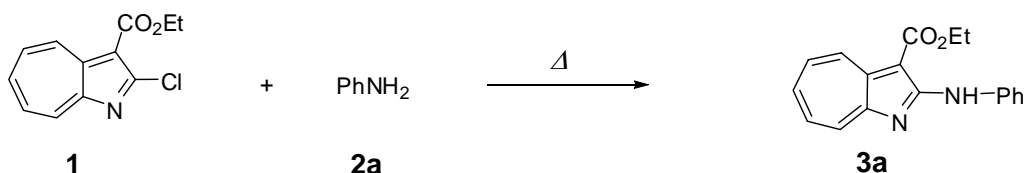
Abstract – The palladium catalyzed heteroarylamination of ethyl 2-chloro-1-azaazulene-3-carboxylate was achieved using a catalyst based on Pd₂(dba)₃ / Xantphos system. Treatment of ethyl 2-(heteroarylamino)-1-azaazulene-3-carboxylates with a PPA-POCl₃ mixture gave corresponding annulation products. 2-(2-Benzothiazolylamino)-1-azaazulene (**3h**) showed anticancer activity against HeLa S3 cells (IC₅₀: 6.5 μM).

In recent years Pd-catalyzed amination of aryl halides has attracted attention,¹ because aryl amines have a potential functionality in pharmaceutical drug candidates.²⁻⁶ The chemistry of azaazulenes⁷ is of interest for their physiological properties^{8,9} as well as physical and chemical properties. Therefore, it is expected that heteroarylamino-1-azaazulenes have potential bioactivities.

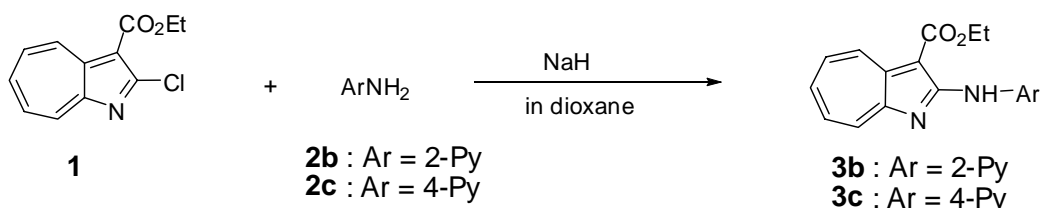
It is known that ethyl 2-chloro-1-azaazulene-3-carboxylate (**1**) reacted with good nucleophile, such as

[†] Dedicated to the memory of late Dr. John Daly.

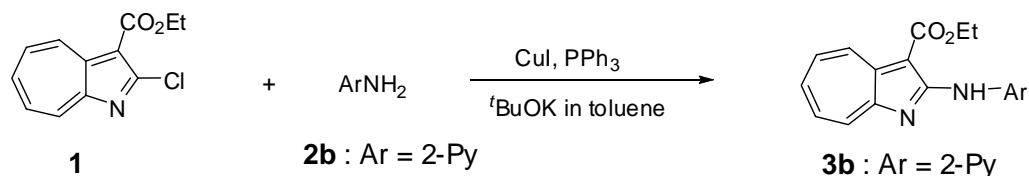
alkoxide, amine, and sulfoxide, to give corresponding 2-substituted-1-azaazulenes.⁷ Indeed, when **1** was treated with aniline (**2a**) in EtOH under reflux for 30 min, ethyl 2-anilino-1-azaazulene-3-carboxylate (**3a**) was obtained in 88% yield. Whereas, the reaction of **1** with inferior nucleophile did not undergo well, and reactions of **1** with 2-aminopyridine (**2b**) or 4-aminopyridine (**2c**) did not give corresponding substituted products.



Therefore, we tried to use pyridinium aminide as superior nucleophile, which was produced by treating aminopyridine with NaH in dioxane under argon atmosphere. Reaction of **1** with 2-aminopyridine (**2b**) in the presence of NaH in dioxane at 120 °C for 24 h gave a complex mixture, and a trace amount of **3b** was isolated along with **1** (47%). On the other hand, when **1** was treated with 4-aminopyridine (**2c**) in the presence of NaH in dioxane for 6 h at 140 °C, **3c** was isolated in 40% yield.



Recently, metal-catalyzed cross coupling of aryl halides with amines are extensively investigated. Therefore, we adopted metal catalyzed amination of 2-chloro-1-azaazulene. At first, Ullmann-type Cu-mediated cross coupling^{10,11} was examined. Treatment of **1** with **2b** in the presence of CuI, PPh₃, and ^tBuOK in toluene gave a complex mixture, and **3b** was obtained only 1% yield together with **1** (55%).



Next, we examined Pd-mediated amination.¹ It is known that Pd₂(dba)₃-catalyzed amination of aryl halides in the presence of Xantphos as a ligand is excellent method.^{12,13} Therefore, we treated **1** with **2b** in the presence of Pd₂(dba)₃, Xantphos, and Cs₂CO₃ in dioxane at 120 °C for 24 h, and **3b** was obtained in 72% yield along with **1** (10%). When above reaction was carried out in the presence of ^tBuOK as base, **3b** was obtained in 40% yield together with **1** (7%) and ethyl 2-oxo-1,2-dihydro-1-azaazulene-3-carboxylate (**4**) (15%). Similar reaction of **1** with **2c** in the presence of Pd₂(dba)₃, Xantphos, and Cs₂CO₃ in dioxane at 120 °C for 24 h, gave **3c** in 59% yield.

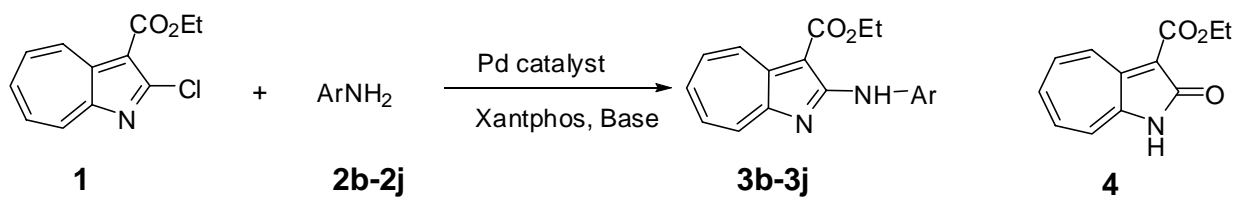
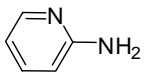
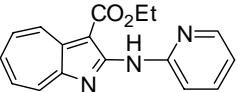
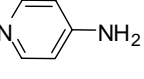
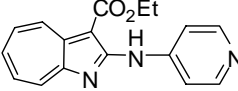
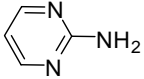
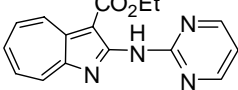
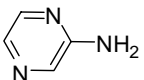
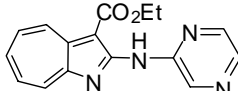
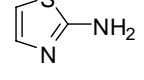
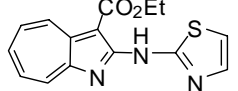
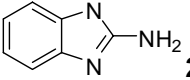
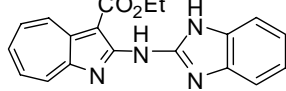
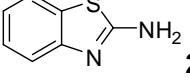
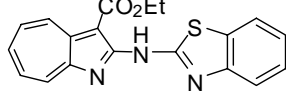
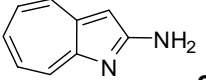
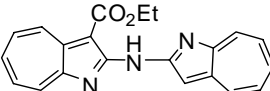
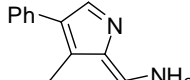
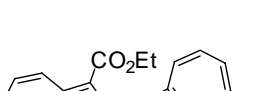
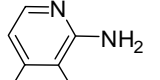
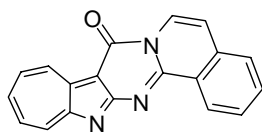
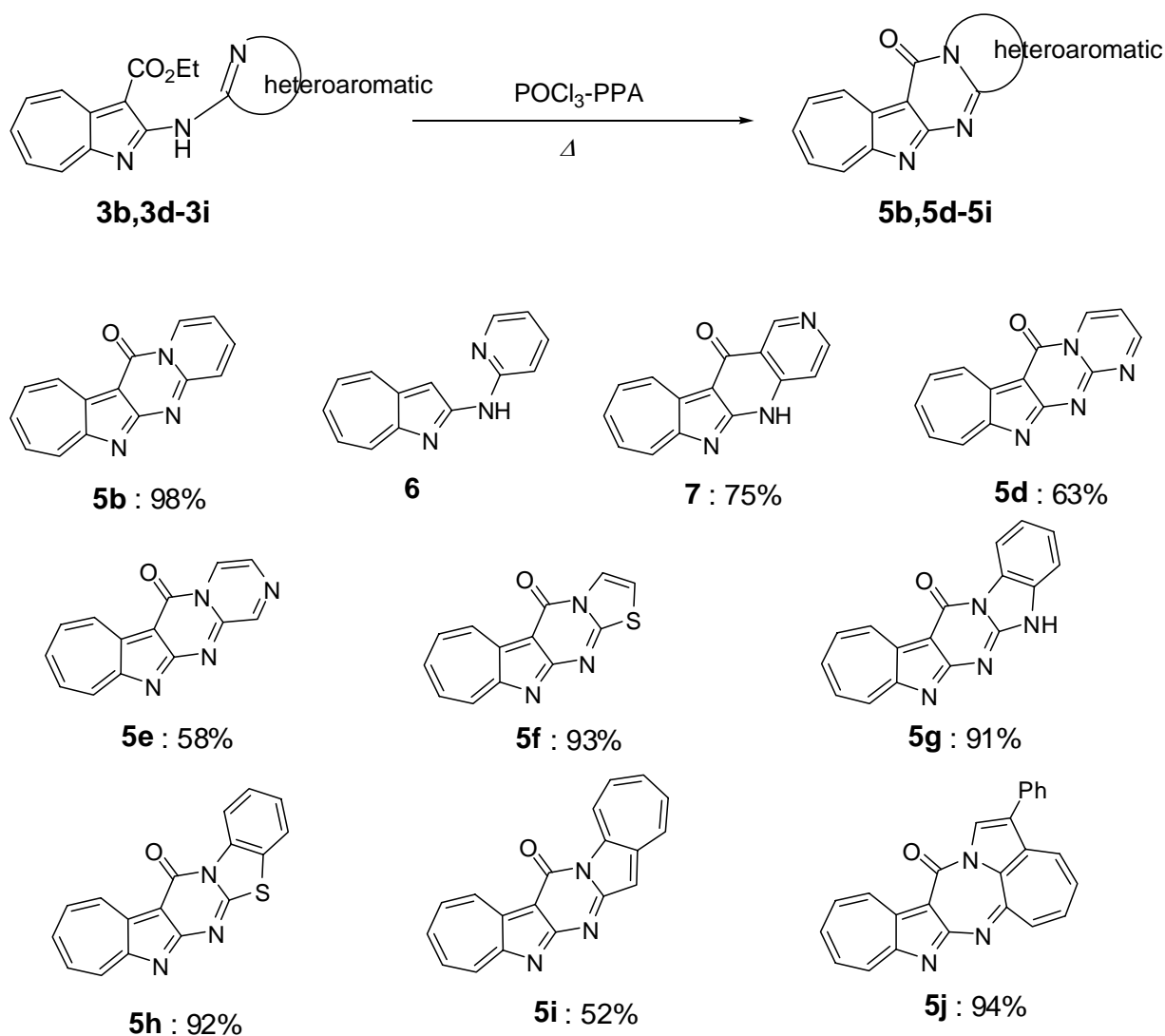


Table 1. Coupling reaction of **1** with heteroaryl amines in the presence of Pd₂(dba)₃, Xantphos, and Cs₂CO₃.

Entry	ArNH ₂	Product	Yield / % (recovery %)
1	 2b		3b : 72 (10)
2	 2c		3c : 59 (-)
3	 2d		3d : 50 (trace)
4	 2e		3e : 73 (-)
5	 2f		3f : 67 (-)
6	 2g		3g : 52 (trace)
7	 2h		3h : 65 (-)
8	 2i		3i : 70 (-)
9	 2j		3j : 52 (-)
10	 2k		5k : 44 (-)

In a similar manner, reactions of **1** with some heteroarylamines were examined.¹⁴ Some results were shown in Table 1. Interestingly, in the reaction of **1** with **2k**, auto-Tandem catalysis¹⁵ occurred and annulated product (**5k**) was obtained in 44% yield in one-pot.

Next, we examined the annulation of **3b-3i**. When **3b** was treated with polyphosphoric acid (PPA) at 150 °C for 5 h, cyclized product (**5b**) was obtained in 83% yield together with 2-(2-pyridylamino)-1-azaazulene (**6**) (10%), which was a deestrication product. For enhance the annulation yield, we treated **3b** with POCl₃-PPA mixture at 150 °C for 5 h, and obtained **5b** in 98% yield. Similar treatment of **3c-3j** gave corresponding annulated products (**7** and **5d-5j**) in moderate to good yields.¹⁶



Some newly synthesized products (**3d**, **3g**, **3h**) were evaluated for their anticancer activity (cytotoxic activity) against HeLa S3 cells. The IC₅₀ values [μ M] are summarized in Table 2. In a case (denoted >), the minimum inhibitory concentration could not be determined due to limited solubility of the

compound in the testing medium. The results revealed that the compound (**3h**) showed moderate activity and the compound (**3d**) showed weak activity against HeLa S3 cells (It is considered that $IC_{50} > 30 \mu M$ is inactive).

Table 2. Cytotoxic evaluation of compounds (**3d**, **3g**, **3h**) expressed in μM .

	3d	3g	3h
IC_{50}	23 ± 3	>7.5	6.5 ± 1.4

In summary, the Pd-mediated coupling of ethyl 2-chloro-1-azaazulene-3-carboxylate (**1**) with wide range of heteroaryl amines was described. Annulation of ethyl heteroaryl amino-1-azaazulene-3-carboxylates using a $POCl_3$ -PPA mixture is useful for preparing new numerical heterocycles. Some ethyl heteroaryl amino-1-azaazulene-3-carboxylates showed anticancer activity against HeLa S3 cells.

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14. *A representative procedure of the amination:* A mixture of **1** (0.2228 g, 0.95 mmol), 2-aminobenzo-thiazol (**3e**) (0.1402 g, 0.093 mmol), Xantphos (0.0533 g, 0.0092 mmol), Pd₂(dba)₃ (0.0580 g, 0.0063 mmol), Cs₂CO₃ (0.3176 g, 0.980 mmol), and dry 1,4-dioxane (2.5 mL) in a sealed tube under argon atmosphere was heated at 120 °C for 22 h under stirring, then water (20 mL) was added. The mixture was extracted with CHCl₃. The extract was dried over Na₂SO₄, and evaporated. Chromatography of the residue with EtOAc-hexane (1 : 8) gave **3h** (0.2106 g, 65%). **3h** : Orange needles (from CH₂Cl₂-hexane), mp 177-178 °C; ¹H NMR (CDCl₃) δ 10.71 (1H, s, NH), 9.09 (1H, d, *J* = 10.0, H-4), 8.48 (1H, d, *J* = 9.6, H-8), 7.82 (1H, d, *J* = 8.0, H-7'), 7.81 (1H, dd, *J* = 10.0, 9.6, H-7), 7.77 (1H, dd, *J* = 10.0, 9.6, H-5), 7.74 (1H, dd, *J* = 7.2, 1.2, H-4'), 7.71 (1H, dd, *J* = 10.0, 9.6, H-6), 7.43 (1H, t, *J* = 7.2, H-5'), 7.27 (1H, ddd, *J* = 8.0, 7.2, 1.2, H-6'), 4.53 (2H, q, *J* = 7.2, CH₂), 1.52 (3H, t, *J* = 7.2, CH₃); ¹³C NMR (CDCl₃) δ 165.2, 161.7, 159.4, 159.2, 149.6, 147.1, 135.1, 133.7, 133.5, 133.3, 133.2, 132.7, 126.0, 123.1, 121.0, 120.5, 99.1, 60.7, 14.7; ν_{max} / cm⁻¹ 1653 (C=O), 3249 (NH); λ_{max} nm (log ε) 277 (4.59), 308 (4.45, sh), 393 (4.78), 444 (3.71, sh). *Anal.* Calcd for C₁₉H₁₅N₃O₂S: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.73; H, 4.32; N, 11.88.
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16. *A representative procedure of the annulation:* A mixture of **3h** (0.0735 g, 0.21 mmol), PPA (5 mL), and POCl₃ (1.5 mL) was heated at 150 °C for 4 h under stirring, and then ice-water (20 mL) was added. The mixture was neutralized with Na₂CO₃. Then the precipitate was collected by filtration, and **5h** (0.0589g, 92%) was obtained. **5h** : Yellow prisms (CHCl₃-EtOH), mp 259-261 °C; ¹H NMR (DMSO-*d*₆) δ 9.50 (1H, dd, *J* = 9.2, 1.6, H-12), 9.08 (1H, dd, *J* = 8.4, 1.2, H-1), 8.84 (1H, dd, *J* = 10.0, 1.6, H-8), 8.32-8.24 (3H, m, H-9,11,12), 8.10 (1H, dd, *J* = 8.4, 1.2, H-4), 7.66 (1H, ddd, *J* = 8.4, 7.6, 1.2, H-3), 7.58 (1H, ddd, *J* = 8.4, 7.6, 1.2, H-2); ¹³C NMR (TFA-*d*) δ 172.2, 159.1, 158.9, 151.7, 147.7, 144.6, 144.6, 144.4, 144.0, 137.6, 136.2, 131.1, 130.9, 125.4, 124.6, 121.9, 103.7; ν_{max} / cm⁻¹ 1690 (C=O); λ_{max} nm (log ε) 288 (4.27), 322 (4.45), 375 (3.60, sh), 458 (3.14). *Anal.* Calcd for C₁₇H₉N₃OS: C, 67.31; H, 2.99; N, 13.85. Found: C, 67.25; H, 3.22; N, 14.11.