HETEROCYCLES, Vol. 79, 2009, pp. 319 - 324. © The Japan Institute of Heterocyclic Chemistry
Received, 30th July, 2008, Accepted, 1st September, 2008, Published online, 1st September, 2008.
DOI: 10.3987/COM-08-S(D)6

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

Kazuya Koizumi,[1] Kunitaka Shimabara,[2] Aya Takemoto,[2] Shinya Yamazaki,[1] Noriko Yamauchi,[1] Hiroyuki Fujii,[3] Masaki Kurosawa,[4] Takeo Konakahara,[4] and Noritaka Abe[1]*

[1] Applied Molecular Bioscience, Graduate School of Medicine, and Department of Biology and Chemistry, Faculty of Science, Yamaguchi University, Yoshida, Yamaguchi 753-8512, Japan

[2] Department of Chemistry, Faculty of Science, Yamaguchi University, Yoshida, Yamaguchi 753-8512, Japan

[3] Science Research Center, Yamaguchi University, Yamaguchi 753-8512, Japan

[4] Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science, Noda, Chiba 278-8510, Japan

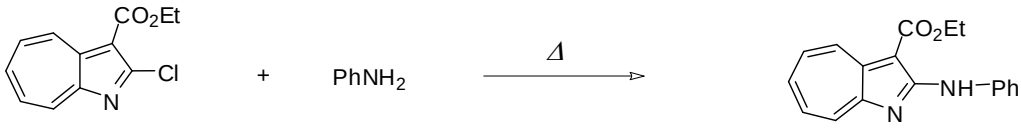
Abstract – The palladium catalyzed heteroarylamination of ethyl 2-chloro-1-azaazulene-3-carboxylate was achieved using a catalyst based on $Pd_2(dba)_3$ / Xantphos system. Treatment of ethyl 2-(heteroarylamino)-1-aza-azulene-3-carboxylates with a PPA-$POCl_3$ mixture gave corresponding annulation products. 2-(2-Benzothiazolylamino)-1-azaazulene (**3h**) showed anticancer activity against HeLa S3 cells (IC_{50}: 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.[2,3,4,5,6] The chemistry of azaazulenes[7] 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

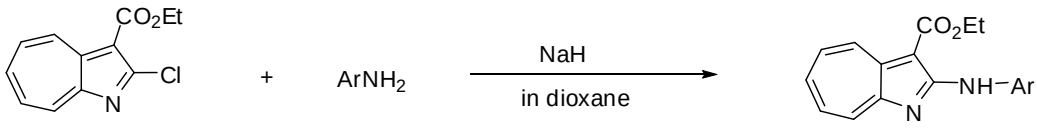
† Dedicated to the memory of late Dr. John Daly.

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.



1 **2a** **3a**

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 ℃ 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 ℃, **3c** was isolated in 40% yield.

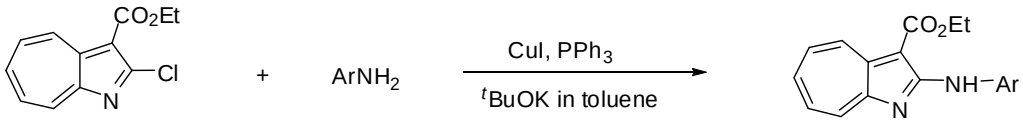


1

2b : Ar = 2-Py
2c : Ar = 4-Py

3b : Ar = 2-Py
3c : Ar = 4-Py

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, PPh_3, and ^{t}BuOK in toluene gave a complex mixture, and **3b** was obtained only 1% yield together with **1** (55%).

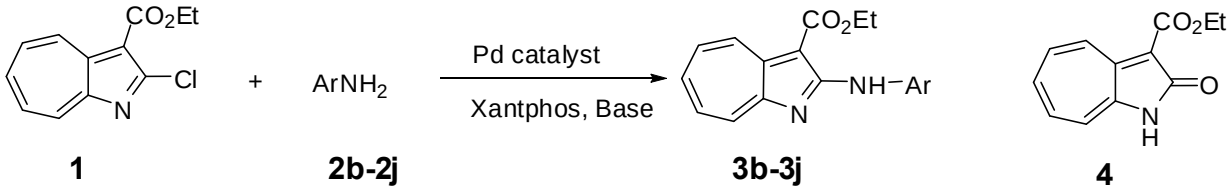


1

2b : Ar = 2-Py

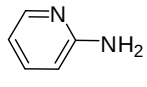
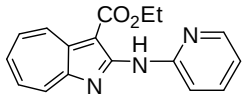
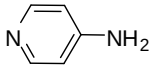
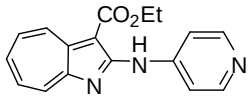
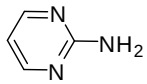
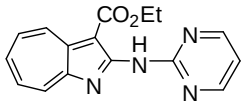
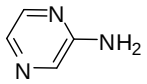
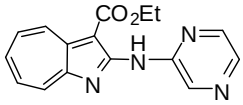
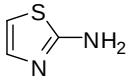
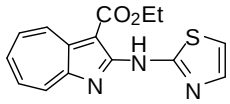
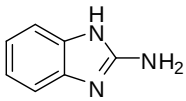
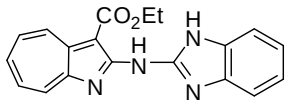
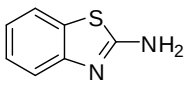
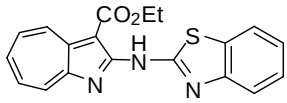
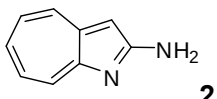
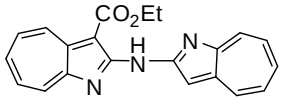
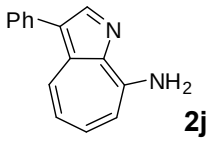
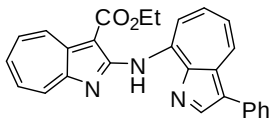
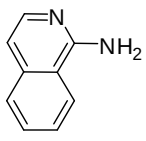
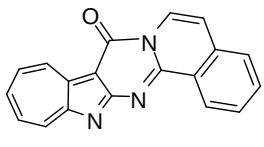
3b : Ar = 2-Py

Next, we examined Pd-mediated amination.[1] It is known that $Pd_2(dba)_3$-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 $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 in dioxane at 120 ℃ for 24 h, and **3b** was obtained in 72% yield along with **1** (10%). When above reaction was carried out in the presence of ^{t}BuOK as base, **3b** was obtained in 40% yield together with **1** (7%) and ethyl 2-oxo-1,2-dihydro-1-azaazulene-3-crboxylate (**4**) (15%). Similar reaction of **1** with **2c** in the presence of $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3 in dioxane at 120 ℃ for 24 h, gave **3c** in 59% yield.



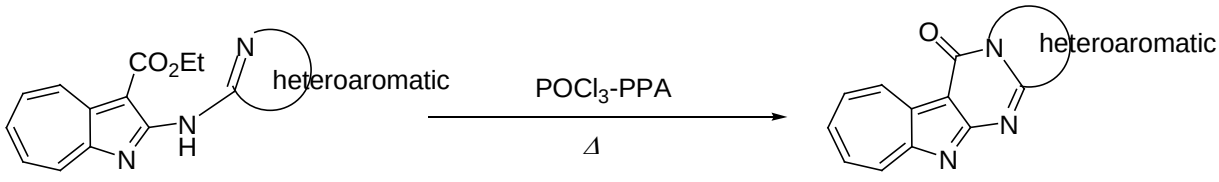
1 **2b-2j** **3b-3j** **4**

Table 1. Coupling reaction of **1** with heteroaryl amines in the presence of $Pd_2(dba)_3$, Xantphos, and Cs_2CO_3.

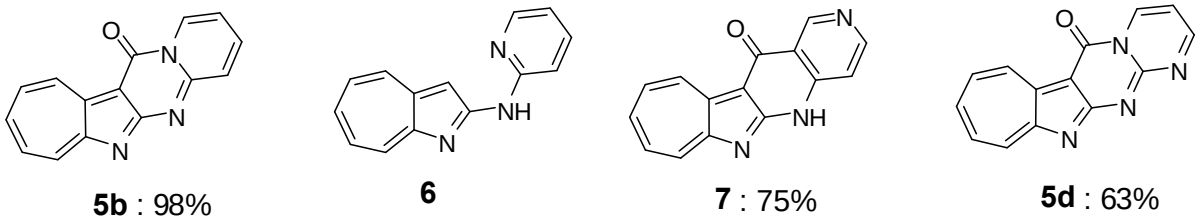
Entry	$ArNH_2$	Product	Yield / % (recovery %)
1	 **2b**		**3b** : 72 (10)
2	 **2c**		**3c** : 59 (-)
3	 **2d**		**3d** : 50 (trace)
4	 **2e**		**3e** : 73 (-)
5	 **2f**		**3f** : 67 (-)
6	 **2g**		**3g** : 52 (trace)
7	 **2h**		**3h** : 65 (-)
8	 **2i**		**3i** : 70 (-)
9	 **2j**		**3j** : 52 (-)
10	 **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 catalysis[15] occurred and annulated product (**5k**) was obtained in 44% yield in one-pot.

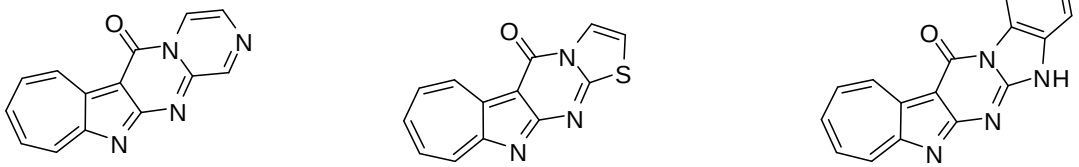
Next, we examined the annulation of **3b**-**3i**. When **3b** was treated with polyphosphoric acid (PPA) at 150 ℃ for 5 h, cyclized product (**5b**) was obtained in 83% yield together with 2-(2-pyridylamino)-1-azaazulene (**6**) (10%), which was a deestrification product. For enhance the annulation yield, we treated **3b** with $POCl_3$-PPA mixture at 150 ℃ 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]



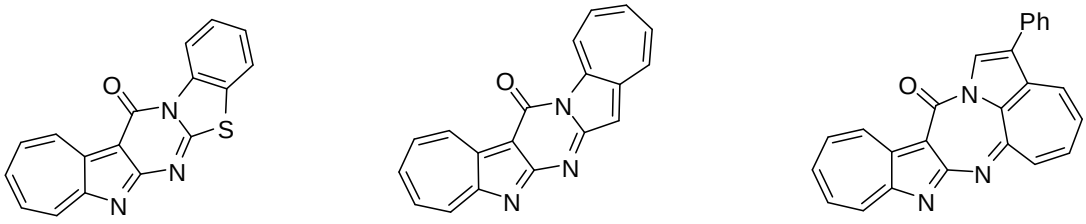
3b,3d-3i **5b,5d-5i**



5b : 98% **6** **7** : 75% **5d** : 63%



5e : 58% **5f** : 93% **5g** : 91%



5h : 92% **5i** : 52% **5j** : 94%

Some newly synthesized products (**3d**, **3g**, **3h**) were evaluated for their anticancer activity (cytotoxic activity) against HeLa S3 cells. The IC_{50} values [μM] 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 μM 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 heteroarylamines was described. Annulation of ethyl heteroarylamino-1-azaazulene-3-carboxylates using a $POCl_3$-PPA mixture is useful for preparing new numerical heterocycles. Some ethyl heteroarylamino-1-azaazulene-3-carboxylates showed anticancer activity against HeLa S3 cells.

REFERENCES AND NOTES

1. For the reviews on the Pd-catalyzed amination reactions, see (a) J. F. Hartwig, *Angew. Chem. Int. Ed.*, 1998, **37**, 2046; (b) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805; (c) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; D. Prim, J.-M. Campagne, D. Joseph, and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041.
2. D. Lednicer, *Strategies for Organic Drug Synthesis and Design*; John Wiley and Sons, New York, 1998.
3. S. Tasler, J. Mies, and M. Lang, *Adv. Synth. Catal.*, 2007, **349**, 2286.
4. R. Jiang, D. Duckett, W. Chen, J. Habel, Y. Y. Ling, P. Lograsso, and T. M. Kamenecka, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6378.
5. W. Huang, W. Zheng, D. J. Urban, J. Inglese, E. Sidransky, C. P. Austin, and C. J. Thomas, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5783.
6. P. Ballard, B. C. Barlaam, R. H. Bradbury, A. Dishington, L. F. A. Hennequin, D. M. Hickinson, I. M. Hollingsworth, J. G. Kettle, T. Klinowska, D. J. Oglivie, S. E. Pearson, J. S. Scott, A. Suleman, R. Whittaker, E. J. Williams, R. Wood, and L. Wright, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6326.
7. For reviews see, N. Abe, '*Recent Research Developments in Organic and Bioorganic Chemistry*' 2001, **4**, 14, Transworld Research Network; T. Nishiwaki and N. Abe, *Heterocycles*, 1981, **15**, 547; M. Kimura, *Yuki Gosei Kagaku Kyokai Shi*, 1981, **39**, 690.
8. T. Ishikawa and A. Zeimoto, *Jpn. Kokai Tokkyo Koho*, JP 1999, 11,255,746.

9. M. Nagahara, J. Nakano, M. Miura, T. Nakamura, and K. Uchida, *Chem. Pharm. Bull.*, 1994, **42**, 2491.
10. For reviews see, S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400.
11. Z. Lu, R. J. Twieg, and S. D. Huang, *Tetrahedron Lett.*, 2003, **44**, 6289, and references therein.
12. J. Yin, M. M. Zhao, A. Huffman, and M. McNamara, *Org. Lett.*, 2002, **4**, 3481.
13. S. B. Larsen, B. Bang-Andersen, T. N. Johansen, and M. Jϕrgensen, *Tetrahedron*, 2008, **64**, 2938.
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), $Pd_2(dba)_3$ (0.0580 g, 0.0063mmol), Cs_2CO_3 (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 $CHCl_3$. The extract was dried over Na_2SO_4, and evaporated. Chromatography of the residue with EtOAc-hexane (1 : 8) gave **3h** (0.2106 g, 65%). **3h** : Orange needles (from CH_2Cl_2-hexane), mp 177-178 °C; ^{1}H NMR ($CDCl_3$) 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, CH_2), 1.52 (3H, t, J = 7.2, CH_3); ^{13}C NMR ($CDCl_3$) 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 $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.73; H, 4.32; N, 11.88.
15. C. Mayers, G. Rombouts, K. T. J. Loones, A. Coelho, and B. U. W. Maes, *Adv. Synth. Catal.*, 2008, **350**, 465.
16. *A representative procedure of the annulation:* A mixture of **3h** (0.0735 g, 0.21 mmol), PPA (5 mL), and $POCl_3$ (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 Na_2CO_3. Then the precipitate was collected by filtration, and **5h** (0.0589g, 92%) was obtained. **5h** : Yellow prisms ($CHCl_3$-EtOH), mp 259-261 °C; ^{1}H 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); ^{13}CNMR (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 $C_{17}H_9N_3OS$: C, 67.31; H, 2.99; N, 13.85. Found: C, 67.25; H, 3.22; N, 14.11.