HETEROCYCLES, Vol. 99, No. 2, 2019, pp. 1361 - 1365. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 10th September, 2018, Accepted, 11th October, 2018, Published online, 18th December, 2018
DOI: 10.3987/COM-18-S(F)69

EFFICIENT SYNTHESIS OF BENZOFURAN FUSED 1-AZAAZULENE

Hiroyuki Fujii,[a]* Yusuke Hironaka,[b] and Noritaka Abe[c]

[a] Science Research Center, Yamaguchi University, Yamaguchi 753-8512, Japan. [b] Graduate School of Science and Engineering, Yamaguchi University, Yamaguchi 753-8512, Japan. [c] Professor Emeritus, Yamaguchi University. E-mail: fujii@yamaguchi-u.ac.jp

Abstract – The synthesis of benzofuran fused 1-azaazulene (cyclohepta[*d*]benzo[4,5]furano[2,3-*b*]pyrrole) (**4**) was achieved by one pot reaction of 2-chloro-1-azaazulene (**1**) with 2-iodophenol (**2**) under the conditions in the presence of $Pd(OAc)_2$ and without using a ligand.

In recent years, we have studied the chemistry of 1-azaazulenes, which are non-alternant conjugated heterocyclic systems, and discuss their interesting chemical and structural features and functionality, and pharmaceutical properties.[1] We reported that polycyclic heterocycles having 1-azaazulene moiety showed several biological activities.[2]

Compounds having a furan skeleton are widely present in nature and are known to exhibit many biological activities. As an example, malibatol A[3] extracted from the leaves of *Hopea malibato* has cytotoxicity against stem cells (CEMSS) and popolohuanone E[4] isolated from phonpei sponge Dysidea are selective for cells of the lung tumor to show toxicity.

As a result of such research, synthesis of pharmacologically active compounds has also been reported, including immunosuppressive action[5] and cyclin dependent kinase inhibitory action,[6] etc.

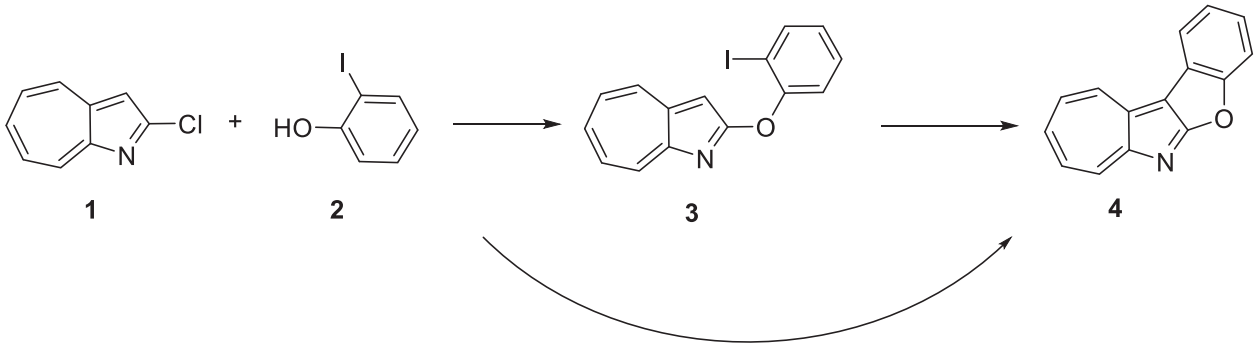
From these facts, it has been found that a compound having a furan skeleton can be used as a magic bullet for diseases which are difficult to treat, which can be said to be a useful compound for mankind. Therefore, aiming at further development of medicine and agriculture, research on various methods for constructing the furan skeleton has been advanced for many years.[7] In recent years, the development of reactions using transition metal catalysts accelerated the construction of furan-fused polycyclic systems.

The furan derivative has a synthetic value as described above, therefore it is expected that furan-fused 1-azaazulenes could have interesting activities including pharmacological activity.

Hitherto, thiophene-ring[8] or pyrrole-ring[9] fused at a 5-membered ring of 1-azaazulene were achieved by intramolecular cyclization reaction of a mercapto group or an amino group to the ethynyl moiety on the

1-azaazulenes. However, these methods could not be used for 1-azaazulene derivatives fused with a furan skeleton. Recently, the problem has also been solved another methods, thus the synthesis of furan-1-azaazulene derivative was achieved by a coupling reaction between 2-chloro-1-azaazulene (**1**) and 2-iodophenol (**2**) followed by the cyclization.[10]

It is considered that establishment of this method gives a large breakthrough in this area, and the synthesis some other 1-azaazulene derivatives fused with the furan skeleton such as **4** could be made possible. However, this method requires as expensive transition metal catalyst and XantPhos as a ligand, and requires long reaction time such as 144 h to achieve high yield. In addition, formation of the intermediate (**3**) was prior, accordingly step-wise operation was forced. For improvement of the reaction, we adopted the reaction conditions without using a ligand.[11]



A mixture of 2-chloro-1-azaazulene (**1**) and 2-iodophenol (**2**) in the presence of Pd catalyst and AcONa in the solvent was heated at 110 °C resulting in the desired product **4**, which was easily isolated by silica gel column chromatography (solvent: ethyl acetate / chloroform 1: 3) from the reaction mixture.

When the reaction was performed for 3 h in the presence of $Pd(OAc)_2$ in dimethylacetamide (DMAc), **4** was obtained in 36% yield. Highest yield (64%) was gained when heating for 24 h, and prolonged heating suppressed the yield (144 h, 53%) (Entry 1-3). When DMF was used as the solvent, the yield was not improved (Entry 4).

When using Pd/C as Pd catalyst in the reaction, the similar result as Entry 1 was obtained in spite of spending long time (24 h, 37%) (Entry 5). Using $Pd_2(dba)_3$ as Pd catalyst, which was used in the cyclization of **3**,[10] did not improve the yield (Entry 6).

Through these reactions, recovery of **1** was not observed and the formation of only trace of **3** was detected in some cases. The results suggested that the transition state would be the cyclization of **3** to **4**, but the reaction conditions made facilitate the cyclization of **3**.

For the expansion of the reaction, we tried the reactions of **1** with 2-hydroxypyridine, 3-hydroxypyridine, 4-hydroxypyridine and 2-naphthol as phenol analogues, but all the reaction did not proceed. Next, a

synthesis of pyrrole fused azaazulene was attempted by reaction of 2-chloro-1-azaazulene (**1**) with aniline or 2-aminopyridine in a similar process, but the reaction also did not proceed. Unfortunately, the reaction was limited on the synthesis of **4** from 2-chloro-1-azaazulene (**1**) with 2-iodophenol (**2**). Nevertheless, the reaction have advantages that the reaction was performed in one pot, using relatively inexpensive $Pd(OAc)_2$ among palladium catalysts and no-using expensive phosphorus-containing ligands like XantPhos.

Still more improvement and expansion of survey are now proceeding.

Table 1. The cyclization of **1** and **2**[a]

entry	Pd catalyst	solvent	time (h)	yield of **4**[b]
1	$Pd(OAc)_2$	DMAc	3	36
2	$Pd(OAc)_2$	DMAc	24	64
3	$Pd(OAc)_2$	DMAc	144	53
4	$Pd(OAc)_2$	DMF	24	55
5	Pd/C	DMAc	24	37
6	$Pd_2(dba)_3$	DMAc	24	47

[a] Reaction conditions: **1** (0.1 mmol), **2** (1.2 equiv.), Pd catalyst (5 mol%), and AcONa (2.0 equiv.) were dissolved in solvent (3 mL) and the mixture was heated under Ar atmosphere. [b] Isolated yield.

EXPERIMENTAL

Mps are measured using a Yanagimoto micro-melting apparatus and uncorrected. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400S (400 MHz) and ^{13}C NMR were recorded on a Bruker AVANCE 400S (100.6 MHz) using deuteriochloroform as a solvent and tetramethylsilane as an internal standard; *J* values are recorded in Hz. IR spectra were recorded for KBr pellets on a Nicolet FT-IR Impact 410 otherwise stated. Electronic spectra were recorded with Shimadzu UV-1600PC spectrophotometer. Mass spectra (ESI-MS) were taken with JEOL JMS-T100CS. GC-Mass spectra were taken with Shimadzu GC-MS QP2010 Plus. Elemental analyses were taken with a Perkin Elmer 2400II. Kieselgel 60 was used for column chromatography and Kieselgel 60G was used for thin-layer chromatography.

Synthesis of cyclohepta[*d*]benzo[4,5]furano[2,3-*b*]pyrrole (4)

Under argon atmosphere, a mixture of **1** (16.4 mg, 0.10 mmol), 2-iodophenol (**2**) (26.4 mg, 0.12 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), and AcONa (16.4 mg, 0.20 mmol) in DMAc (3 mL) was stirred for 24 h at 110 °C. The reaction mixture was poured into water (50 mL), and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, AcOEt/$CHCl_3$=3/1) of the residue gave **4** (14.1 mg, 64%).

4: Red plates (from acetone), mp 165-167 °C; δ_H 7.42-7.44 (m, 2H), 7.67-7.69 (m, 1H), 7.83 (like t, *J* 10.0 Hz, 1H), 7.88 (like t, *J* 8.8, Hz, 1H), 7.94 (like t, *J* 10.4 Hz, 1H), 8.00-8.02 (m, 1H), 8.76 (d, *J* 9.2 Hz, 1H), 8.82 (d, *J* 9.6 Hz, 1H); δ_C 110.3, 112.6, 120.8, 122.8, 123.9, 125.5, 129.2, 130.1, 132.0, 134.9, 135.5, 136.3, 159.9, 160.9, and 178.6; ν_{max}/cm^{-1} 1181 (-O-); λ_{max} (MeCN) nm (log ε) 303 (4.57), 372 (3.77), 390 (3.88), and 478 (3.07); *m/z* (rel intensity) 219 (M^+, 100). HRMS (ESI^+): Calcd for $C_{15}H_9NNaO$: 242.0582; Found: *m/z* 242.0514. *Anal*. Calcd for $C_{15}H_9NO$: C, 82.18; H, 4.14; N, 6.39. Found: C, 81.80; H, 3.91; N, 6.40.

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