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SYNTHETIC METHODS FOR PREPARING 1,3-DI(2-PYRIDYL)-AZULENE

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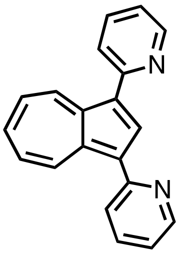
Abstract – The title compound was synthesized either by introduction of another pyridine ring into 3-(2-pyridyl)-1,2,3,8-tetrahydroazulen-1-one or by Stille and Negishi double cross-coupling reactions of 1,3-dihaloazulenes with the corresponding 2-pyridyl reagents.

INTRODUCTION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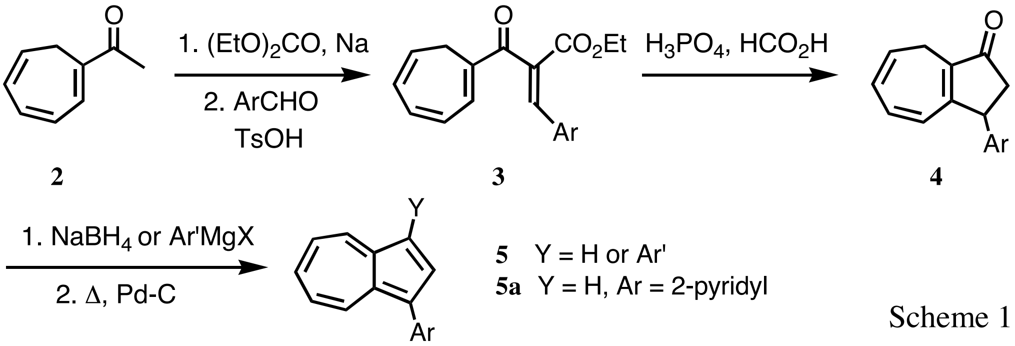
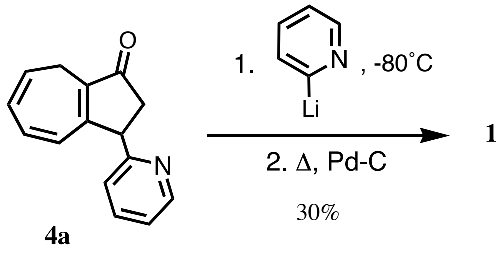
Recently Wakabayashi *et al.* reported syntheses and spectroscopic properties of pyridylazulenes, some of which, including the title compound (**1**), were found to be useful as pH indicators[1] and the paper prompts us to describe our independent synthetic efforts for preparing **1**.[2] We had previously developed a synthetic route from 1-acety-1,3,5-cycloheptatriene (**2**) to 1-aryl- and 1,3-diarylazulenes (**5**).[3] This method was applicable to synthesize 1-(2-pyridyl)azulene (**5a**) as shown in Scheme 1. We have extended the method and also applied the double cross-coupling reactions of 1,3-dihaloazulenes for preparing **1**.[4] Experimental details are now disclosed herein.



Scheme 1

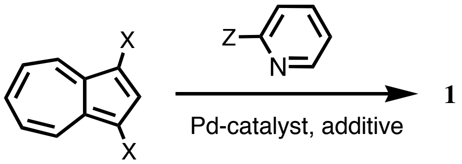
RESULTS AND DISCUSSION

One method is starting from 3-(2-pyridyl)-1,2,3,8-tetrahydroazulen-1-one (**4a,** Ar = 2-pyridyl in **4**) as shown in Scheme 1. Addition of 2-pyridyllithium to **4a** and subsequent dehydration and oxidation with palladium-carbon in refluxing diphenyl ether provided **1** in 30% yield (Scheme 2). The yield was improved neither by replacing 2-pyridyllithium to the corresponding Grignard reagent nor by modification of the oxidation step using quinones as an oxidant. Then, we applied Pd-catalyzed double cross-coupling reactions[4] to access to **1**. The results of the coupling using 1,3-dibromo- and 1,3-diiodoazulenes (**6a** and **6b**) are shown in Table 1. Under the Stille coupling conditions modified by Fu *et al.*,[5] the yield of **1** was low (entry 1) and addition of cupric oxide in this reaction, reported by Gronowitz,[6] was found effective. Unusually the yield of **1** from **6a** was slightly better than that from **6b** (entries 2, 3). Although an excess amount of the zinc reagent was required to complete the reaction under the Negishi coupling conditions, the yield of **1** from **6b** (entry 5) was superior to that (35%) reported by Wakabayashi *et al.*[1]



Scheme 2

Table 1. Results of cross-coupling reactions of 1,3-dihaloazulenes



6a; X = Br, **6b**; X = I

Entry	X	Z	Reaction Conditions	Yield of **1**(%)
1	Br	$SnBu_3$	$Pd_2(dba)_3$, $(t\text{-}Bu)_3PHBF_4$, CsF, dioxane, 80°C, 24 h	31
2	Br	$SnBu_3$	$Pd(PPh_3)_4$, CuO, DMF, 120°C, 4 h	66
3	I	$SnBu_3$	$Pd(PPh_3)_4$, CuO, DMF, 120°C, 4 h	60
4	Br	ZnBr	$Pd(PPh_3)_4$, THF, 25°C, 30 h	46
5	I	ZnBr	$Pd(PPh_3)_4$, THF, 25°C, 24 h	88

SUMMARY

We have demonstrated synthetic methods for preparing 1,3-di(2-pyridyl)azulene (**1**). The multi-step sequence from 1-acety-1,3,5-cycloheptatriene (**2**) to **1**, previously developed by us, was found inefficient because of the low yield of **1**. The Pd-catalyzed double cross-coupling using 2-pyridylzinc bromide provided a satisfactory yield of **1**.

EXPERIMENTAL

A THF solution of 2-pyridylzinc bromide, cesium fluoride, tris(dibenzylideneacetone)dipalladium [$Pd_2(dba)_3$] and tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] were purchased from Aldrich Inc. 2-(Tri-*n*-butylstannyl)pyridine was purchased from Frontier Scientific, Inc., 2-bromopyridine was from Tokyo Kasei Industry, Inc., and cupric oxide and tri-*tert*-butylphosphine were from Kanto Chem. Industry, Inc. The starting materials, 3-(2-pyridyl)-1,2,3,8-tetrahydroazulen-1-one (**4a**)[3] and 1,3-dihloazulenes (**6**)[7] were prepared by the literature method. See ref. 4 for spectroscopic methods.

1,3-Di(2-pyridyl)azulene (1) from 3-(2-pyridyl)-1,2,3,8-tetrahydroazulen-1-one (4a): To a solution of 2-bromopyridine (395 mg, 2.50 mmol) in 15 mL of Et_2O at –80°C under nitrogen atmosphere was added dropwise 3.1 mL of an *n*-BuLi (1.2 M in hexane), then followed by addition of 330 mg (1.50 mmol) of **4a** in 5 mL of Et_2O. After being stirred at the same temperature for 2 h, the reaction mixture was poured into 50 mL of water and extracted three times with 50 mL of Et_2O. The combined organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed and the residual was dissolved in 4 mL of diphenyl ether. To this solution was added 50 mg of 10% Pd-carbon and the mixture was refluxed for 1 h. After being cooled, the resulted mixture was directly chromatographed on alumina (eluted with hexane and then EtOAc/hexane = 1/9) to give 132 mg (30% yield) of **1**[1] as a blue oil. ^1H NMR ($CDCl_3$) $\delta = 7.18$ (td, J= 4.8, 1.6 Hz, 2H), 7.37 (t, J= 9.8 Hz, 2H), 7.71 (t. J= 9.8 Hz, 1H), 7.78 (m, 4H), 8.58 (s, 1H), 8.76 (dm, J= 4.0 Hz, 2H), 9.55 (d, J= 9.8 Hz, 2H). UV-Vis (CH_3OH) λ_{max} = 220 (log ε = 4.22), 258 (4.28), 311 (4.56), 387 (3.99), 544sh (2.44), 579 (2.54), 639sh (2.41), 708sh (1.83) nm.

1,3-Di(2-pyridyl)azulene (1) by the Stille cross-coupling reaction of 1,3-dihaloazulenes with $Pd_2(dba)_3$ and (t-Bu)$_3PHBF_4$: A mixture of 286 mg (1.00 mmol) of **6a**, 810 mg (2.20 mmol) of 2-(tri-*n*-butylstannyl)pyridine and 0.67 g (4.4 mmol) of cesium fluoride in 5 mL of dioxane was evacuated well. To this was added 46 mg (0.050 mmol) of $Pd_2(dba)_3$ and 30 mg (0.010 mmol) of (t-Bu)$_3PHBF_4$ and this mixture was heated at 80°C under argon atmosphere for 24 h. The resulted dark brown reaction mixture was poured into 50 mL of saturated aqueous $NaHCO_3$ solution and extracted three times with 30 mL of Et_2O. The combined organic layer was washed with brine and was dried with $MgSO_4$. The solvent was removed and the residue was purified by alumina chromatography to give 87 mg (31%) of **1**.

1,3-Di(2-pyridyl)azulene (1) by the Stille cross-coupling reaction of 1,3-dihaloazulenes with $Pd(PPh_3)_4$ and CuO: The reaction was carried out similarly by the aforementioned way with using 1.0 mmol of **6**, 0.05 mmol of $Pd(PPh_3)_4$ and 1.0 mmol of CuO in 8mL of DMF. The reaction mixture was poured into a mixture of KF and EtOH and solids formed were removed by filtration through a Celite®

pad. The filtrate was diluted with 100 mL of Et_2O and was extracted three times with 50 mL of 6M HCl solution. The combined acid solution was made basic with a 40% solution of NaOH and was extracted with three times with 40 mL of Et_2O. The combined organic layer was washed with brine and was dried with $MgSO_4$. The solvent was removed and the residue was purified by alumina chromatography. The yields are shown in Table 1.

1,3-Di(2-pyridyl)azulene (1) by the Negishi cross-coupling reaction of 1,3-dihaloazulenes: A mixture of 1.0 mmol of **6**, 24 mL (12 mmol) of 2-pyridylzinc bromide solution and 10 mL of THF was evacuated well. To this solution was added 31 mg (0.050 mmol) of $Pd(PPh_3)_4$ and this mixture was stirred at rt under argon atmosphere. The resulted dark brown reaction mixture was poured into 70 mL of water and extracted three times with 30 mL of Et_2O. The combined organic layer was washed with brine and was dried with $MgSO_4$. The solvent was removed and the residue was purified by alumina chromatography. The yields are shown in Table 1.

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