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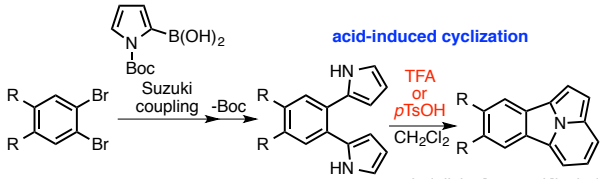

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Facile synthesis of indolizino[3,4,5-*ab*]isoindoles by an acid-induced cyclization of 1,2-di(1*H*-pyrrol-2-yl)benzenes

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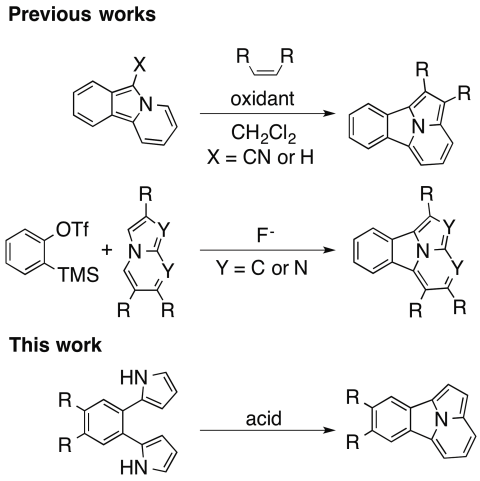
ABSTRACT

The new synthetic method of indolizino[3,4,5-*ab*]isoindoles (INIs) by an acid-induced intramolecular cyclization of 1,2-di(1*H*-pyrrol-2-yl)benzenes has been developed. This protocol can be applied to the preparation of INI derivatives with electron–donating and –withdrawing groups as well as a⊗✔INIs.

1. Introduction

Cycl[3.2.2]azine is amine-type nitrogen-bridged [10]annulene with a planar structure and was firstly reported in 1958.[1] Cycl[3.2.2]azine derivatives are 10π-electron aromatic compounds with high fluorescence efficiency[2] and wide range of biological activity.[3] Indolizino[3,4,5-*ab*]isoindoles (INIs) have an additional benzene ring at 1,2-position of cycl[3.2.2]azine and were reported in 1986.[4] INIs exhibit high fluorescent quantum yields in blue to green regions suitable for OLED materials and sensor devices. INI derivatives and these metal complexes as emission layers for OLED, thus, show excellent device performances.[5] Previously reported synthetic strategies of INIs were based on the cyclization between pyrido[2,1-*a*]isoindoles or indolizines and electron-deficient alkynes or alkenes (Scheme 1). Unsubstituted INI was initially synthesized from 6-cyanopyrido[2,1-*a*]isoindole with dimethyl acetylene dicarboxylate (DMAD), followed by decarboxylation.[4] Unsubstituted pyrido[2,1-*a*]isoindole also reacted with DMAD or electron-deficient olefins in the presence of oxidants to afford INIs.[6] In 2007, Xu reported the cycloaddition of indolizine with benzynes to give INI derivatives in moderate yields.[7] Furthermore, benzo[*a*]imidazo-[5,1,2-*cd*]indolizines and 2,3,9-triazocyclopenta[*j*,*k*]fluorenes were obtained from imidazo[1,2-*a*]pyridines and imidazo[1,2-*a*]pyrimidines, respectively, reacted with benzynes under microwave irradiations.[8] While the introduction of the substituents and benzannulation at indolizine positions of INIs have been successful with these methods, the substitution at peripheral benzene ring (6, 7, 8 and 9-positions) has scarcely been reported to date. Therefore, the development of a wide scope synthetic method for INIs is highly required.



Scheme 1. Synthetic routes of INI derivatives

Di(1*H*-pyrrol-2-yl)benzenes have three regioisomers. Among them, 1,3- and 1,4-di(1*H*-pyrrol-2-yl)benzenes are known to

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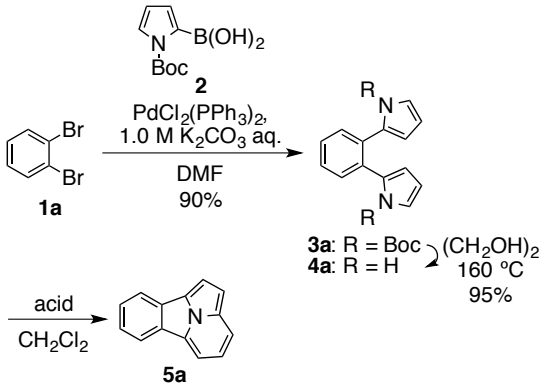
be useful raw materials for the preparation of expanded porphyrins,[9] calixpyrroles,[10] pyrrole-based oligomers[11] and polymers.[12] On the other hand, heterocycles-substituted benzenes at *ortho*-positions can be often used as the precursors for the expanded aromatic compounds by photocyclizations or Scholl reactions.[13] We noted that the reactivity of 1,2-di(1*H*-pyrrol-2-yl)benzene has been scarcely investigated except for the synthesis of 1,2-di(1*H*-pyrrol-2-yl)benzene-based calixpyrroles.[14] Therefore we have investigated the synthesis of the pyrrole-based aromatic compounds from 1,2-di(1*H*-pyrrol-2-yl)benzene. In this context, we found that acid-catalyzed intramolecular cyclization of 1,2-di(1*H*-pyrrol-2-yl)benzenes gave INI derivatives. Herein, we report the facile synthetic method toward the preparation of 7,8-substituted INI derivatives and, 7- and 9-azaINIs. The single crystal X-ray diffraction analyses, optical and electrochemical properties and DFT calculations of these INI derivatives are also reported.

2. Synthesis and Characterizations

Scheme 2 shows the synthetic route of INI **5a** from 1,2-dibromobenzene **1a**. The key intermediate of 1,2-di(1*H*-pyrrol-2-yl)benzene **4a** was synthesized from 1,2-dihalobenzenes (X = Br or I), independently reported by three groups.[14, 15, 16] We have modified the reaction conditions for improvement of the yields of **4a**. *o*-Bis[1-(*t*-butoxycarbonyl)-pyrrolyl]benzene **3a** was prepared by a Suzuki-Miyaura coupling reaction of **1a** with 1-(*t*-butoxycarbonyl)-pyrrole-2-boronic acid **2**. The optimized reaction conditions using **2** (5 eq.), $PdCl_2(PPh_3)_2$ and 1.0 M K_2CO_3 aq. in DMF at 80 ºC afforded **3a** in 90% yield. Deprotection of Boc groups at 160 ºC in ethylene glycol gave **4a** in 95% yield. The structure of **4a** was confirmed by single crystal X-ray diffraction analysis (Figure S1). The addition of *p*-toluenesulfonic acid (*p*TsOH; 5 eq.) to a solution of **4a** in CH_2Cl_2 gave yellow-colored compound after purification by silica gel column chromatography eluted with hexane. From ^1H and ^{13}C NMR spectra, ^1H-^1H COSY spectrum and mass spectrum, we assigned this yellow compound as INI **5a** (Table 1, entry 2). Finally, the structure of **5a** was confirmed by single crystal X-ray diffraction analysis (Figure S2). In order to improve the yields, various acidic conditions have been investigated (Table 1). When decreasing the amount of *p*TsOH to 1 eq. (entry 1), the reaction did not proceed and **4a** was recovered in 81% yield. In contrast, when the amount of *p*TsOH was increased to 10 eq. (entry 3), **4a** was consumed. However, **5a** was obtained only in 1% probably because of the decomposition of generated INI. Next, other Brønsted acids were attempted. With 1 eq. of trifluoroacetic acid (TFA), **5a** was obtained only in a trace amount (entry 4). However, with 5 eq. of TFA, the yield of **5a** was drastically improved to 63% (entry 5). On the other hands, 10 eq. of TFA lowered the yield to 17% (entry 6). For trichloroacetic acid (TCA), 50 eq. of the acid was necessary to complete the reaction due to the lower acidity of TCA than that of TFA (entry 7-9). Lewis acids only gave the decomposed or polymeric products (entry 10-12), which suggested the protonation at pyrrole is necessary for the cyclization reaction. A plausible reaction mechanism is shown in Scheme S1.

On the basis of the optimized conditions, this acid-cyclization method was adapted to 4,5-substituted 1,2-di(1*H*-pyrrol-2-yl)benzenes (**4b**–**4d**) and di(1*H*-pyrrol-2-yl)pyridines (**7** and **10**) (Scheme 3). Compounds **4b**, **4c** and **4d** were synthesized by Suzuki-Miyaura coupling conditions as same as **4a** from the corresponding *o*-dibromobenzenes. The acid-induced cyclization reactions of **4b** and **4c** proceeded by the similar conditions to synthesize **5a**, giving corresponding INIs **5b** (46%) and **5c** (28%), respectively. However, **5c** was gradually decomposed under ambient conditions in solution and at the solid state. On the other hand, 1,2-di(1*H*-pyrrol-2-yl)benzene **4d** with electron-withdrawing group showed lower reactivity compared with **4a**. When using 5 eq. of TFA, **5d** was obtained in a very low yield, while using 10 eq. of TFA, the yield of **5d** increased up to 39%. Subsequently, we have attempted the synthesis of nitrogen atoms incorporated azaINIs **8** and **11** from 3,4-di(1*H*-pyrrol-2-yl)pyridine **7** and 2,3- di(1*H*-pyrrol-2-yl)pyridine **10**. Compounds **7** and **10** were prepared from **6** and **9** by Suzuki-Miyaura coupling. The crystal structure of **7** is shown in Figure S4. Firstly, the cyclization reaction was examined with TFA in CH_2Cl_2 as same as **5a**, but starting material was only recovered. Secondly, *p*TsOH was used instead of TFA because *p*TsOH is stronger acid than TFA, but this reaction also gave only starting material. Finally, we found that the cyclization reactions of **7** and **10** proceeded in the presence of *p*TsOH (20 eq.) in 1,2-dichloroethane under reflux conditions. Although these substrates of **7** and **10** are possible to form two regioisomeric compounds **8a** and **8b**, and **11a** and **11b**, respectively, these reactions gave only **8a** and **11a** in 6% and 3%, respectively, and compounds **8b** and **11b** were not obtained.

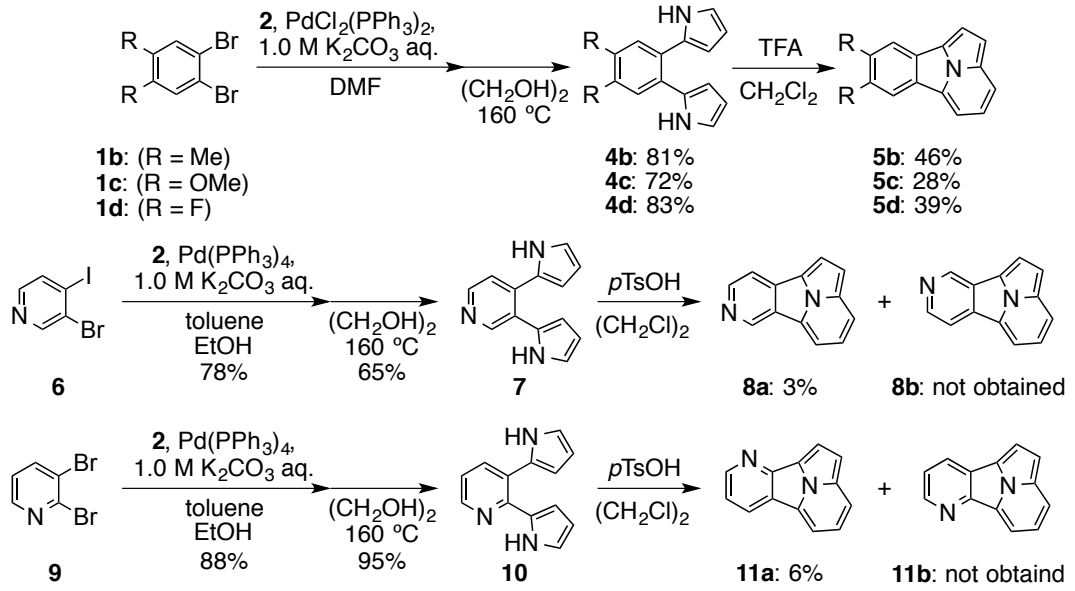


Scheme 2. Synthesis of INI **5a**

Table 1. Reaction conditions of acid cyclization reaction

entry	acid (eq.)	Times (h)	Yield (%)	**4a** (%)
1	*p*TsOH (1)	0.5	3	81
2	*p*TsOH (5)	0.5	6	21
3	*p*TsOH (10)	0.5	1	0
4	TFA (1)	0.5	trace	90
5	TFA (5)	0.5	63	11
6	TFA (10)	0.5	17	0
7	TCA (1)	0.5	0	98
8	TCA (5)	0.5	3	86
9	TCA (50)	1	20	14
10	BF_3•OEt_2 (10)	3	0	0
11	$FeCl_3$ (10)	3	0	0
12	$AlCl_3$ (10)	3	0	0

Acid cyclization reactions were carried out with **4a** (0.06 mmol) and acid in refluxed CH_2Cl_2 (3 ml)



Scheme 3. Synthesis of INI derivatives.

The UV-vis absorption and emission spectra of the obtained INI derivatives in CH_2Cl_2 are shown in Figure 1 and Table 2. The absorption peaks of **5b** were observed at 425 nm and 448 nm, which were red-shifted by 1 nm from **5a**, while the absorption of **5c** blue-shifted by 3 nm in CH_2Cl_2. The absorption of azaINIs of **8a** and **11a** exhibited hypsochromic shift that the longest absorption peaks were observed at 430 nm for **8a** and 440 nm for **11a**.

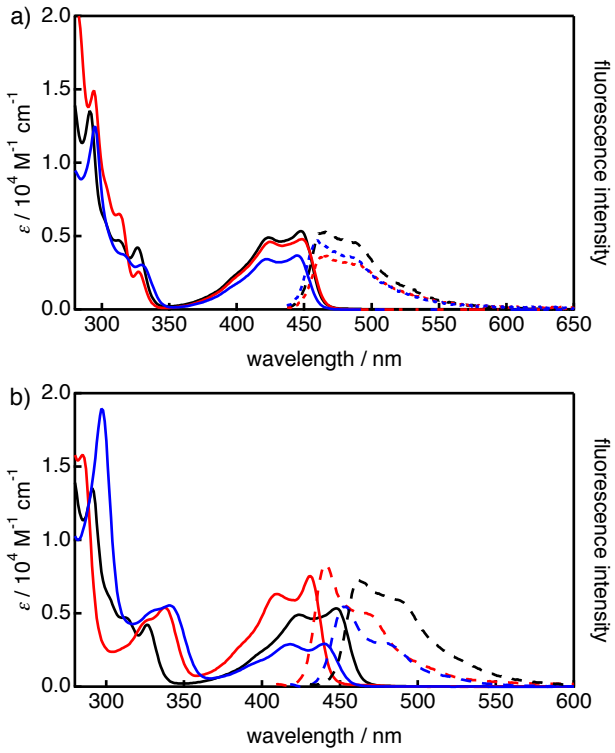


Figure 1. UV-vis absorption (solid line) and fluorescence (dashed line) spectra of a) **5a** (black), **5b** (red) and **5d** (blue), and b) **5a** (black), **8a** (red) and **11a** (blue) in CH_2Cl_2

Table 2. Photophysical properties of INI derivatives in CH_2Cl_2.

	λ_{abs} / nm (ε / 10^3 M^{-1} cm^{-1})	λ_{fl} / nm (λ_{ex} / nm)	Φ_{fl}
5a	326 (4.2), 424 (4.9), 447 (5.0)	465 (424)	0.40
5b	327 (2.6), 425 (4.6), 448 (4.8)	467 (425)	0.36
5d	329 (3.2), 422 (3.6), 445 (3.9)	464 (422)	0.30
8a	337 (5.4), 409 (6.3), 430 (7.5)	441 (409)	0.46
11a	341 (5.5), 418 (2.9), 440 (2.9)	454 (418)	0.30

The newly prepared INI derivatives showed fluorescence and the trends of maximum peak positions were similar to absorption characters. The fluorescence peaks were observed at 465 nm for **1a**, 467 nm for **1b**, 464 nm for **1d**, 441 nm for **8a** and 454 nm for **11a** with moderate fluorescence quantum yields (Φ_f = 0.30-0.46). The Φ_f of INI derivatives showed the solvent dependency (Figure S5-S9).[5a] In DMSO, the fluorescence emission quantum yields were obtained with highest values of 0.75 for **5a**, 0.64 for **5b**, 0.67 for **5d**, 0.63 for **8a** and 0.52 for **11a**. Such solvent effects are similar to the other reported INI derivatives.

To elucidate the structure and electronic properties of these INIs, we have performed DFT calculations at B3LYP/6-31G* level by Gaussian 09 program (Figure 2).[17] The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of INIs **5a, 5b, 5d, 8a, and 11a** are expanded to the INI main structure which results are similar to the previous report.[5a] The properties of substituents affected the HOMO and LUMO levels of INIs. The HOMO and LUMO levels of **5b** are slightly higher than those of **5a** because methyl group works as electron–donating group. On the other hand, **5d**, **8a** and **11a** exhibit the lower HOMO and LUMO levels

since fluorine and nitrogen atoms are electron–withdrawing groups.

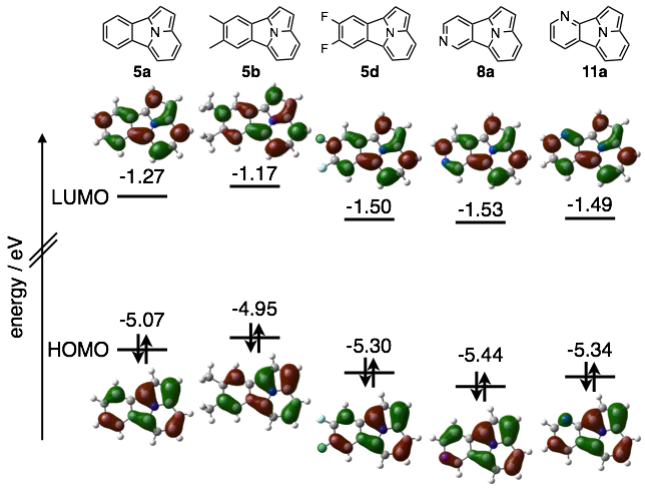


Figure 2. Energy diagrams and Kohn-Sham molecular orbitals of **5a**, **5b**, **5d**, **8a** and **11a**.

In conclusion, we have succeeded in the facile synthesis of INI derivatives by the acid-induced cyclization from 1,2-di(1*H*-pyrrol-2-yl)benzenes. This method makes it possible to synthesize INIs only by 3 steps from commercially available dibromobenzenes so that the various functional groups were easily introduced on benzene parts. Extensions of this synthetic method to other functional groups and heterocycles-included INIs are actively in progress in our laboratory.

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Supplementary Material

Supplementary data (synthetic detail, characterization, optical properties and X-ray diffraction analysis) associated with this article can be found, in the online version.