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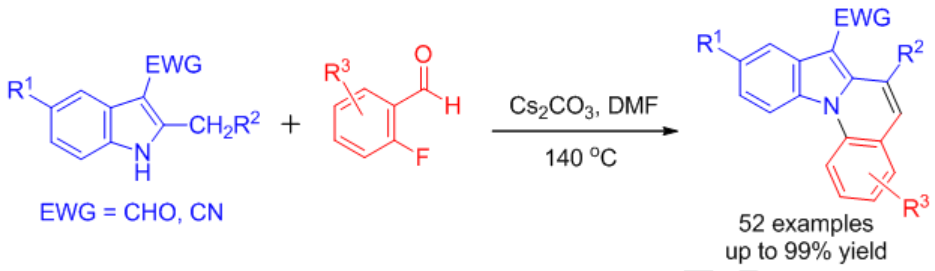

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ABSTRACT

A simple and efficient one-pot synthesis of substituted indolo[1,2-*a*]quinolines under transition-metal-free conditions has been developed. When 2-fluorobenzaldehyde was treated with substituted 2-methylindoles in the presence of Cs_2CO_3, the desired products were typically obtained in good to excellent yields. This reaction sequence involves a nucleophilic aromatic substitution and a Knoevenagel condensation reaction. Our mechanistic investigation revealed that both reactions could proceed as an intermolecular reaction in the first step.

Fused nitrogen containing heterocycles are frequently found in bioactive natural products and synthetic compounds. Among them, compounds containing indolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]quinoline (Figure 1) have been reported to possess antibacterial, antifungal,[1] anti-proliferative[2] and apoptosis inducing properties.[3] In addition, some are used as organic semiconductors,[4] and organic sensitizers for solar cells.[5] These compounds have drawn considerable attention as a result of these interesting properties. Numerous synthetic methods have recently been reported, mostly on pyrrolo[1,2-*a*]quinoline derivatives.[6]

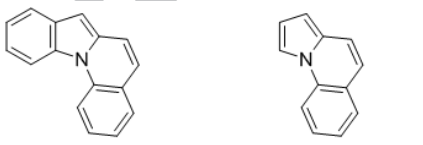
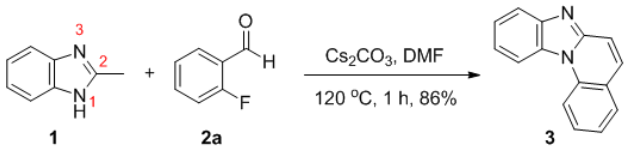


Figure 1. Structures of indolo[1,2-*a*]quinoline and pyrrolo[1,2-*a*]quinoline

Reports on the synthesis of substituted indolo[1,2-*a*]quinolines are limited and typically utilize a transition metal catalyst containing Pd, Rh, Mn or Cu.[7] Other methods include K_3PO_4-mediated reaction of indole-2-carborboaxaldehydes and 2-halophenylacetonitriles,[8] iodine-mediated electrophilic ring closure of 1-(2-(substituted ethynyl)phenyl)indoles,[9] HCOOH-mediated intramolecular azo-Nazarov cyclization,[10] reaction of 2-substituted quinolines and benzyne intermediate,[11] and flash vacuum pyrolysis.[12] Despite no transition-metal catalysts being employed, many of these methods use starting materials that are not easily accessible and require multi-step preparation. In 2013, Yokomatsu and coworkers reported a one-pot synthesis of benzimidazole[1,2-*a*]quinoline (**3**) from 2-methyl-1*H*-benzimidazole (**1**) and 2-fluorobenzaldehyde (**2a**) under transition-metal-free conditions (Scheme 1).[13] This cascade process involved an intermolecular nucleophilic aromatic substitution (S_NAr) reaction followed by an intramolecular Knoevenagel condensation. We were interested in further exploring this method in the synthesis of indolo[1,2-*a*]quinolines from easily accessible starting materials without the need of transitional metal catalysts.



Scheme 1. One-pot synthesis of benzimidazole[1,2-*a*]quinoline (**3**).

Unlike benzimidazole **1**, indole does not contain a nitrogen atom at the 3 position to act as an electron-withdrawing group. Without the presence of this electron-withdrawing group to increase the acidity of the methyl group (CH_3) nearby, the Knoevenagel condensation is unlikely to occur. Therefore, we

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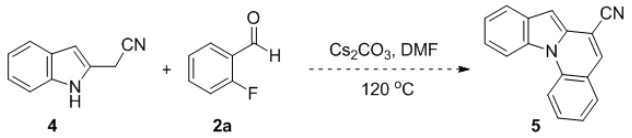
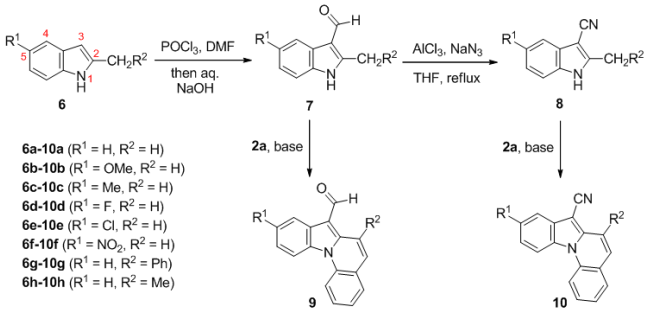
initially attempted to employ 2-(cyanomethyl)indole (**4**)[14] bearing an electron-withdrawing group (CN) as a starting material for this synthesis under the reaction conditions reported by Yokomatsu (base = Cs_2CO_3 (3 eq.), solvent = DMF and temperature = 120 °C) (Scheme 2). Unfortunately, this reaction gave a complex mixture of unidentified products.



Scheme 2. Our initial approach to synthesize substituted indolo[1,2-*a*]quinoline **5**.

Alternatively, an electron-withdrawing group could be installed at C3 of the indole substrate. Formyl (CHO) and cyano (CN) groups (Scheme 3) were selected since the former can be easily installed on commercially available indole substrates by a Vilsmeier reaction[15] and the latter can be formed by treating the resulting formyl group with $AlCl_3$ and NaN_3.[16]



Scheme 3. Our approach to synthesize substituted indolo[1,2-*a*]quinolines **9** and **10**.

To our delight, when we treated indolecarboxaldehydes **7a**, **7b** and **7d** with 2-fluorobenzaldehyde (**2a**) under the same reaction conditions, the desired products **9a**, **9b**, and **9d** were obtained in 60%, 80% and 60% yields, respectively. Indole **7b** was then selected as a model substrate to optimize the reaction conditions. Upon switching the base from Cs_2CO_3 to K_2CO_3 or K_3PO_4, the yields of desired product **9b** were decreased to 73% and 40%, respectively. Other bases such as Et_3N and DBU were ineffective. No reaction took place in the presence of Et_3N while DBU gave only a trace amount of **9b**. We further screened different solvents. When DMF was replaced by DMSO, **9b** was obtained in 44% yield whereas toluene and 1,4-dioxane gave only trace amounts of **9b**. We were pleased to discover that the yield was improved to 95% when the temperature was increased from 120 °C to 140 °C (reaction time = 3 h). In addition, the yield was much lower (30%) when the reaction was performed at a lower temperature (100 °C) for the same length of time. Decomposition occurred at a higher temperature (reflux at 153 °C). Based on these results, the optimal reaction conditions were determined to be Cs_2CO_3 as base in DMF at 140 °C.[17]

Next, we explored the scope of the indole substrates by varying the electron-withdrawing group at C3 and the substituents at C2 and C5 on the indole ring (Table 1). We found that the indoles bearing a cyano group (**8**) generally gave higher yields than those bearing a formyl group (**7**), except when R^1 = Cl (entry 13) and R^2 = Me (entry 16). Although the differences might be insignificant, these results were unexpected. It is well known that the methyl group adjacent to a carbonyl group (C=O) is more acidic than that next to a cyano group. Therefore, indole substrates **7** were expected to be more reactive toward the Knoevenagel condensation. In addition, the indole substrate seemed to prefer an electron-donating group at C6. The presence of a methoxy (OMe) or a methyl (Me) group at this position of the indole ring gave the desired products in highest yields (entries 10-11). When R^1 was an electron-withdrawing group (F and Cl), the reaction times were generally longer and the yields were typically lower. In the extreme cases when the indole bearing a very strong electron-withdrawing group (NO_2) was employed (entries 6 and 14), only a trace amount of the desired product was obtained. A likely rational is that the presence of an electron-donating group at C6 can improve the nucleophilicity of the indole nitrogen. As a result, its reactivity increases in the S_NAr reaction. When the methyl group at C3 of the indole substrate was replaced with ethyl (CH_2Me) and benzyl (CH_2Ph) groups, the desired products were also obtained in good yields (entries 7-8 and 15), except when EWG = CN and R^2 = Me (entry 16) due to an isolation problem. It should be noted that the reaction times required for the substrates bearing a benzyl group were much longer than those with an ethyl group possibly due to steric hindrance.

Table 1. Reaction scope of the cascade reaction varying substituents on C5 of the indole substrates[a]

Entry	Indole	R^1	R^2	Time[b]	Product	Yield[c]
1	**7a**	H	H	5 h	**9a**	70%
2	**7b**	OMe	H	3 h	**9b**	95%
3	**7c**	Me	H	3.5 h	**9c**	86%
4	**7d**	F	H	5 h	**9d**	60%
5	**7e**	Cl	H	16 h	**9e**	65%
6	**7f**	NO_2	H	16 h	**9f**	trace
7	**7g**	H	Ph	16 h	**9g**	75%
8	**7h**	H	Me	6 h	**9h**	84%
9	**8a**	H	H	5 h	**10a**	78%
10	**8b**	OMe	H	3 h	**10b**	98%
11	**8c**	Me	H	3.5 h	**10c**	98%
12	**8d**	F	H	5 h	**10d**	85%
13	**8e**	Cl	H	16 h	**10e**	30%
14	**8f**	NO_2	H	16 h	**10f**	trace
15	**8g**	H	Ph	16 h	**10g**	78%
16	**8h**	H	Me	4 h	**10h**	12%[d]

[a]All reactions were performed in the presence of **7** or **8** (200 mg, 1 eq.), 2-fluorobenzalaldehyde (**2a**) (1.6 eq.), and Cs_2CO_3 (3.0 eq.) in DMF (4 mL) at 140 °C

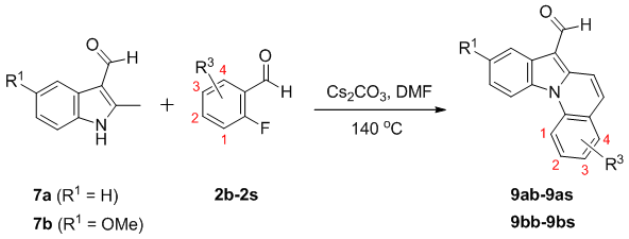
[b]The reaction was terminated after the indole substrate was consumed.

[c]Isolated yield.

[c]Low yield due to an isolation problem.

The scope of the benzaldehyde substrates was also investigated using commercially available benzaldehydes (Table 2). Both electron-withdrawing (F, Cl, Br and I) and electron-donating (OMe and Me) groups were selected. All of the reactions performed in this investigation gave the desired products, which are fluorescent and easily identified on a TLC plate. However, some of the desired products could not be isolated because by-products coeluted with the desired products upon silica gel chromatography. Most of the isolated yields were lower than those employing 2-fluorobenzaldehyde (**2a**) possibly due to the increased steric hindrance. Some of the benzaldehydes

bearing an additional halogen atom at C2 (see numbering system in Scheme 4) also gave low reaction yields (entries 2, 6, and 8). Although none of the by-products were isolated and characterized, we speculated that these low yields might be a result of a competing S_NAr reaction at the 2 position of the benzaldehydes. The likelihood of this is especially high when the halogen atom is F. Installation of the methoxy group on the benzaldehyde substrate was expected to lower its electrophilicity toward the S_NAr reaction. However, it is interesting to note that the reaction between **2p**, **2q** or **2r** with **7b** gave the desired product **9bp**, **9bq** or **9br** in good to excellent yield (entries 33-35).



Scheme 4. Synthesis of substituted indolo[1,2-*a*]quinolines by varying substituents on the benzaldehydes.

Table 2. Reaction scope of the cascade reaction varying substituents on the benzaldehydes[a]

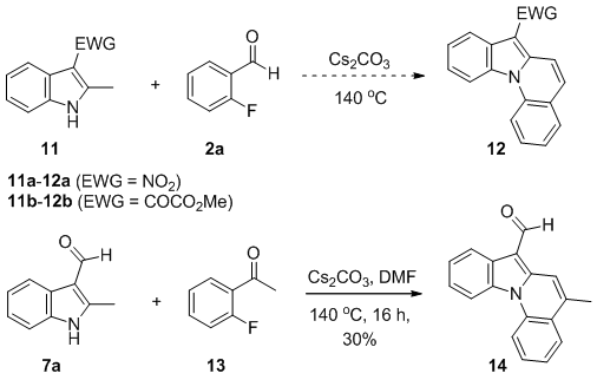
Entry	Indole	Benzal-dehyde	R_3	Time[b]	Product	Yield[c]
1	**7a**	**2b**	1-F	16 h	**9ab**	62%
2	**7a**	**2c**	2-F	16 h	**9ac**	15%
3	**7a**	**2d**	3-F	16 h	**9ad**	29%
4	**7a**	**2e**	4-F	16 h	**9ae**	47%
5	**7a**	**2f**	1-Cl	16 h	**9af**	77%
6	**7a**	**2g**	2-Cl	16 h	**9ag**	40%
7	**7a**	**2h**	3-Cl	16 h	**9ah**	38%
8	**7a**	**2i**	2-Br	16 h	**9ai**	41%
9	**7a**	**2j**	3-Br	16 h	**9aj**	47%
10	**7a**	**2k**	4-Br	16 h	**9ak**	69%
11	**7a**	**2l**	3-I	16 h	**9al**	37%
12	**7a**	**2m**	1-Me	16 h	**9am**	ND
13	**7a**	**2n**	2-Me	16 h	**9an**	55%
14	**7a**	**2o**	3-Me	16 h	**9ao**	33%
15	**7a**	**2p**	1-OMe	16 h	**9ap**	67%
16	**7a**	**2q**	2-OMe	16 h	**9aq**	29%
17	**7a**	**2r**	3-OMe	16 h	**9ar**	ND
18	**7a**	**2s**	4-OMe	16 h	**9as**	29%
19	**7b**	**2b**	1-F	4 h	**9bb**	50%
20	**7b**	**2c**	2-F	4 h	**9bc**	ND
21	**7b**	**2d**	3-F	5 h	**9bd**	45%
22	**7b**	**2e**	4-F	4 h	**9be**	20%
23	**7b**	**2f**	1-Cl	16 h	**9bf**	70%
24	**7b**	**2g**	2-Cl	6 h	**9bg**	84%
25	**7b**	**2h**	3-Cl	9 h	**9bh**	48%
26	**7b**	**2i**	2-Br	4 h	**9bi**	71%
27	**7b**	**2j**	3-Br	5 h	**9bj**	74%
28	**7b**	**2k**	4-Br	5 h	**9bk**	32%
29	**7b**	**2l**	3-I	5 h	**9bl**	17%
30	**7b**	**2m**	1-Me	8 h	**9bm**	51%
31	**7b**	**2n**	2-Me	16 h	**9bn**	ND
32	**7b**	**2o**	3-Me	16 h	**9bo**	71%
33	**7b**	**2p**	1-OMe	4 h	**9bp**	84%
34	**7b**	**2q**	2-OMe	4 h	**9bq**	99%
35	**7b**	**2r**	3-OMe	5 h	**9br**	70%
36	**7b**	**2s**	4-OMe	16 h	**9bs**	29%

[a]All reactions were performed in the presence of **7a** or **7b** (200 mg, 1 eq.), substituted benzalaldehyde **2b-2s** (1.6 eq.), and Cs_2CO_3 (3.0 eq.) in DMF (4 mL) at 140 °C

[b]The reaction was terminated after the indole substrate was consumed.

[c]Isolated yield (ND = % yield not determined due to an isolation problem).

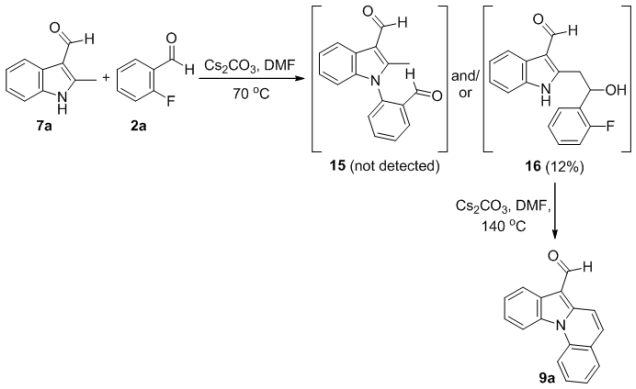
To explore the scope of this reaction as much as possible, other electron-withdrawing groups such as nitro (NO_2)[18] and methyl oxoacetate ($COCO_2Me$)[19] groups were also installed on the indole ring (Scheme 5). Unfortunately, both starting materials (**11a** and **11b**) gave a complex mixture of unidentified products. We also attempted to replace 2-fluorobenzaldehyde with commercially available 2-fluoroacetophenone (**13**). However, the reaction of **7a** with this ketone gave the desired product (**14**) in only 30% yield due to the decreased reactivity of the carbonyl group.



Scheme 5. Our attempts to synthesize substituted indolo[1,2-*a*]quinolines **12** and **14**.

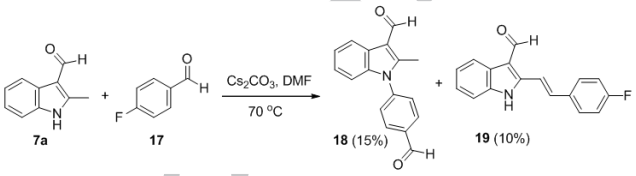
As mentioned earlier in the synthesis of benzimidazole[1,2-*a*]quinoline (**3**) from 2-methyl-1*H*-benzimidazole (**1**) and 2-fluorobenzaldehyde (**2**), Yokomatsu suggested that an intermolecular S_NAr reaction took place first followed by an intramolecular Knoevenagel condensation.[13] However, when Ding and coworkers used a similar benzimidazole substrate (CH_3 was replaced with CH_2CN) to react with 2-iodobenzaldehyde in the presence of K_2CO_3, CuI and L-proline to produce benzimidazole[1,2-*a*]quinoline-6-carbonitrile, they proposed that an intermolecular condensation between the methylene group (CH_2) of the benzimidazole substrate and the formyl group of the benzaldehyde proceeded first followed by a copper-catalyzed intramolecular C-N coupling reaction.[20] Both proposed mechanisms are reasonable since the substrates and the reaction pathways are different. In the latter case, it is possible for the condensation to occur first because the presence of the cyano group can increase the acidity of the methylene group. On the other hand, the substrate in the former case lacks this electron-withdrawing group so the condensation can occur later. In our case, we speculated that the S_NAr reaction should occur before the condensation since the NH of the indole is more acidic than the methyl group at C2. To test our hypothesis, we attempted to

isolate intermediates from the reaction of **7a** and **2a** by lowering the reaction temperature (Scheme 6). When the reaction was carried out at 70 ºC, we were able to isolate only intermediate **16**. In addition, when this intermediate was subjected to the same reaction conditions we typically performed to prepare indolo[1,2-*a*]quinolines, product **9a** was obtained. This is strong evidence in support of the condensation taking place first in the cascade process. However, it is also possible that intermediate **15** also formed and we were just not able to isolate it.



Scheme 6. Attempt to isolate reaction intermediates.

To further investigate the mechanism of this cascade reaction, we simply replaced 2-fluorobenzaldehyde (**2a**) with 4-benzaldehyde (**17**) since the product formed could not undergo cyclization (Scheme 7). In this reaction, compound **18** would be expected if the S_NAr reaction took place whereas compound **19** would be expected if the Knoevenagel condensation occurred. Interestingly, we were able to isolate both compounds in comparable yields. In this reaction, the more stable *trans* isomer **19** was expected to form although our characterization data was not sufficient to definitively identify its geometry. Based on this investigation, we proposed that under our reaction conditions both the intermolecular S_NAr reaction and the intermolecular Knoevenagel condensation can proceed in the first step before the cyclization can occur.



Scheme 7. Nucleophilic aromatic substitution and Knoevenagel condensation reactions of indole **7a** and 4-fluorobenzaldehyde (**17**).

In summary, the synthesis of substituted indolo[1,2-*a*]quinolines via nucleophilic aromatic substitution and Knoevenagel condensation reactions under transition-metal-free conditions has been achieved. Based on our mechanistic investigation, both reactions could proceed as an intermolecular reaction in the first step. In this synthesis, the desired indoloquinoline was obtained in as high as 99% yield when 5-methoxy-2-methyl-1*H*-indole-3-carboxaldehyde and 2-fluoro-3-methoxybenzaldehyde were employed as starting materials.

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Supplementary Material

Experimental procedures and characterization data for **7**-**10** (except those not isolated), **14**, **16**, **18** and **19** are available at……

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Highlights

- A simple and efficient one-pot synthesis of substituted indolo[1,2-*a*]quinolines.
- Up to 99% yield.
- No transition metal catalysts employed.
- Either an S_NAr or a Knoevenagel condensation reaction proceeded in the first step.