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Tröger's base derivative-catalyzed one-step one-pot synthesis of chromenofuroindoles and naphthofuroindoles

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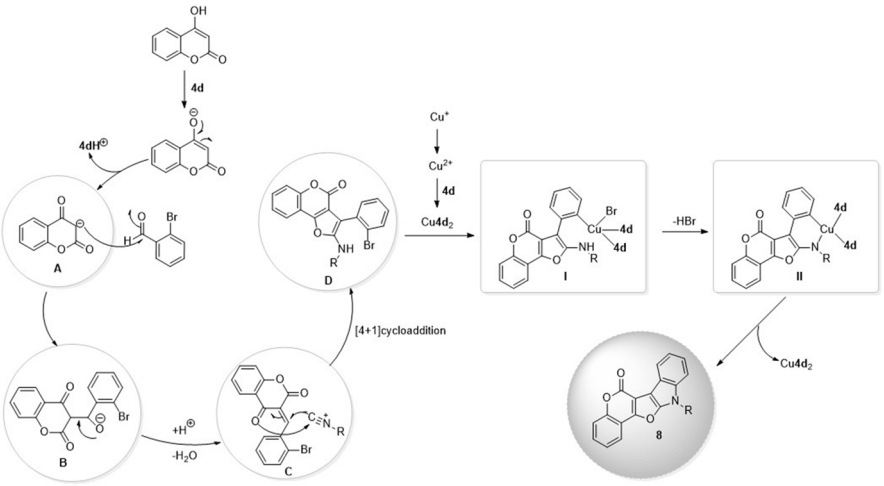
Abstract

A series of N^2,N^8-bis(nitrogen-containing heterocycle)-yl-2,8-dicarboxamide-Tröger's bases were synthesized. The most efficient one, N^2,N^8-di(4*H*-1,2,4-triazol-4-yl)-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-2,8-dicarboxamide (**4d**), was used as bifunctional catalyst to promote the one-step one-pot preparation of the chromeno[3′,4′:4,5]furo[2,3-*b*]indoles or naphtho[2′,3′:4,5]furo[2,3-*b*]indoles with CuI via the cascade Aldol-[4 + 1]cycloaddition-intramolecular Ullmann reaction of 4-hydroxycoumarin (or 2-hydroxy-1,4-naphoquinone), substituted benzaldehydes and isocyanide. A reasonable catalysis mechanism was investigated by the ^{1}H NMR titration and control experiments.

Graphical abstract



Hang Zhou and Ya-wen Sun contributed equally to this work.

Extended author information available on the last page of the article

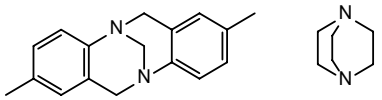
Keywords Tröger's base derivative · Synthesis · Catalysis · Chromeno[3′,4′:4,5]furo[2,3-*b*]indole · Naphtho[2′,3′:4,5]furo[2,3-*b*]indole

Introduction

Furoindole is an important framework of many natural products and synthetic intermediates [1–3] with many biological activities including anti-inflammatory [4], analgesic [5], anti-allergy [6], removing fever [7], and so on. Some furo[2,3-*b*]indole derivatives have also been used as the potent openers of Ca^{2+}-activated K^+ (BK_{Ca}) channels [8] to treat relative diseases [9]. It is important to note that the furo[2,3-*b*]indole derivatives have excellent luminescent properties due to the large conjugation system and plane rigidity. Therefore, their simple and efficient synthesis is of great significance.

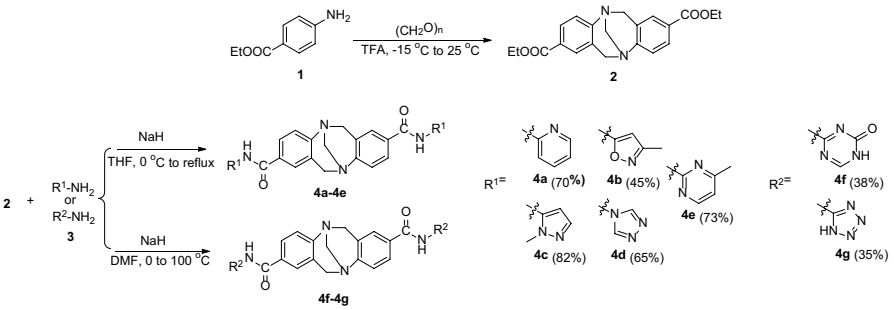
In general, there are three methods to prepare furo[2,3-*b*]indoles: (1) to construct the furan ring based on a functional indole skeleton [10–13]; (2) to form the indole ring from the reactions between anilines and functional furans [14–16]; and (3) to close the ring of opening-chain structures [17]. It is necessary to synthesize at least one substrate in advance in these strategies. Ji and co-workers [18] reported a two-step one-pot reaction, including an isocyanide-based multicomponent reaction (I-MCR) followed by a copper-catalyzed intramolecular Ullmann reaction, to construct the furo[2,3-*b*]indole derivatives. They firstly carried out the reaction of 4-hydroxycoumarin, 4-hydroxy-1-methylquinolinone or 2-hydroxy-1,4-naphthoquinone with aldehyde and isocyanide to give relative furan derivatives at 110 °C in anhydrous toluene for 6–48 h. Without separating and purifying the produced furan derivatives, CF_3COOH (TFA), CuI, L-proline and K_2CO_3 were added in sequentially under nitrogen atmosphere and the mixture was refluxed for another 24 h to afford the target furo[2,3-*b*]indole derivatives by recrystallization from acetone or by silica gel column chromatography. An organic acid L-proline was used as the ligand in the second step. Therefore, it is necessary to develop alkaline ligand for the acid-sensitive substrates. In Ji's work, DABCO (1,4-diazabicyclo[2.2.2]octane) was also found to promote the Cu-catalyzed Ullmann reaction as the ligand, which reminds us of the Tröger's base (TB, Fig. 1) derivatives that also contains two bridge nitrogen atoms.

Because of the unique V-type structure, molecular rigidity and C_2-axial chirality, TB and its derivatives have been applied in fluorescent material [19–22], molecular recognition [23–25], DNA probe [26–28], bionic molecular receptor [29, 30], etc., since the synthesis of TB in 1887. Recently, they become the research focus of



Tröger's base DABCO

Fig. 1 The structure of Tröger's base (stereochemistry not shown) and DABCO



Scheme 1 Synthesis of TB derivatives **4**

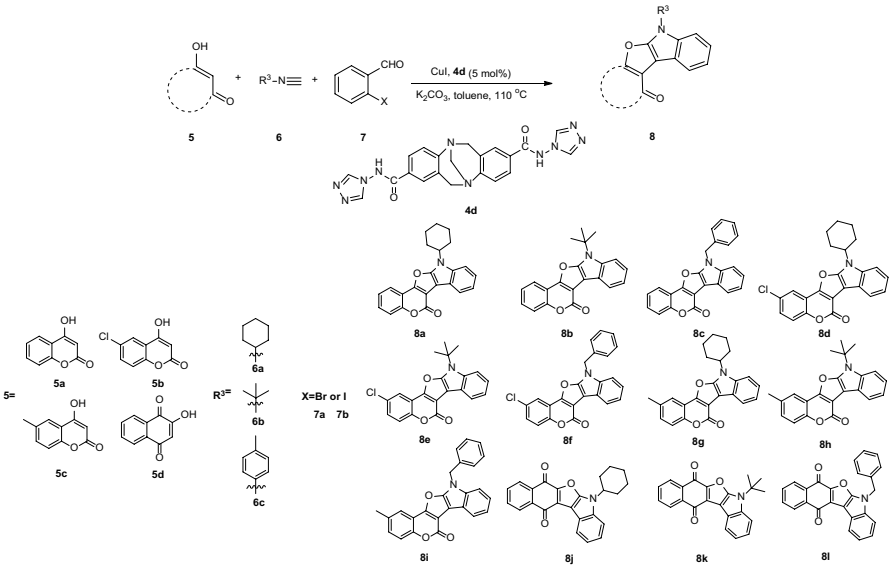
polymer chemistry and gas separation membrane materials [31–36]. However, it is worth noting that the advantages of TB and its derivatives served as catalysts are far from being developed. Enlightened by the unique structure of TB framework, which enables TB and its derivatives to capture appropriate molecules and then shows catalytic activities, we have synthesized several series of TB derivatives by increasing catalytic active sites and basicity and then applied them successfully in organic synthesis as organocatalyst or ligand [37–42].

Amide is the main structural unit of peptide chains. Acting both as a hydrogen bond donor and acceptor, it has been utilized as the main segment of many types of catalysts, especially peptide catalysts [43–48].

In this paper, a series of new TB derivatives (**4**) were synthesized by introducing *N*-heterocycles (including pyridine, pyrimidine, isoxazole, pyrazole, triazole, 1,3,5-triazin-2(1*H*)-one and tetrazole) into TB skeleton through amide bond (Scheme 1). They were used both as the basic catalyst for the Aldol-[4 + 1] cycloaddition and the ligand for the following copper-catalyzed intramolecular Ullmann reaction of coumarins or 2-hydroxy-1,4-naphthoquinone (**5**), isocyanide (**6**) and substituted benzaldehydes (**7**) to promote the real one-pot preparation of the chromeno[3′,4′:4,5]furo[2,3-*b*]indoles or naphtho[2′,3′:4,5]furo[2,3-*b*]indoles (**8**) in good yield (Scheme 2).

Results and discussion

The reaction conditions were optimized based on the yield of **8a** (Table 1). The results showed that the reaction did not occur without catalyst (Table 1, Entry **1**) in toluene. TB derivative **2** (Table 1, Entry **2**) could only afford trace product, while **4a**-**4 g** (Table 1, Entries **3**–**9**) could promote the synthesis of **8a**, in which **4d** gave the best result (61%, Table 1, Entry **6**). When the loading of CuI was 5 mol%, increasing the loading of **4d** from 5 to 10 then 15 mol% only caused 1% increment of the yield of **8a** (Table 1, Entry **6** vs. Entries **10**, **11**). But when the loading of CuI was 10 mol%, adding the loading of **4d** from 5 to 10 mol% led to an increase in the yield of **8a** from 61 to 85% (Table 1, Entry **6** vs. Entry **13**). Based on the principle of economic and environmental benefits, the combination of 10 mol% of **4d** and



Scheme 2 Synthesis of furoindole derivatives **8**

10 mol% of CuI was the best choice. Subsequently, it was found that the highest yield of **8a** was obtained in the presence of K_2CO_3 (2 eq., 85%, Table 1, Entry **13** vs. Entries **16**–**17**). The results also indicated that toluene was the most suitable solvent for the reaction (Table 1, Entry **13** vs. Entries **18**–**20**).

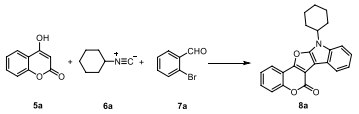
Above all, in the presence of K_2CO_3 (2 eq.), using 10 mol % of **4d** and 10 mol% CuI as catalyst and refluxing in toluene was the optimum condition.

With the optimized conditions in hand, we proceeded to explore the scope of substrates (Table 2). According to the results, in general, coumarins **5a-5c** gave higher yield than 2-hydroxy-1,4-naphthoquinone **5d**. The possible reason is that the deprotonation of **5a-5c** carries out more easily than the latter. As for isocyanides, benzyl isocyanide gave a higher yield of product than tert-butyl-substituted or cyclohexyl-substituted isocyanide, which maybe due to the larger steric hindrance of cyclohexyl and tert-butyl than that of benzyl.

To understand the catalysis mechanism, ^{1}H NMR analysis (400 MHz) was applied to monitor the reaction process. The specific steps were as follows: catalyst **4d** (0.0133 g, 0.3 mmol), **5a** (0.0486 g, 0.3 mmol), **6a** (0.0328 g, 0.3 mmol), **7a** (0.0555 g, 0.3 mmol), CuI (0.0057 g, 10 mol%, 0.03 mmol), K_2CO_3 (0.0829 g, 0.6 mmol) and toluene (15 mL) were added in a 25 mL two-neck round-bottom flask and stirred at 110 °C. 0.50 mL of the mixture was taken out and the solvent was removed under vacuum, and then the residue was dissolved in DMSO-d_6 for NMR analysis. The reaction process was monitored by repeating the operation at five-minute intervals (Fig. 2).

From Fig. 2, as the reaction proceeded, the signal of hydrogen atoms on the amide ($\delta = 11.94$ ppm) and triazole ($\delta = 8.70$ ppm) group of **4d** became weaker gradually. And it is also clear that the signal of three methylene groups ($\delta = 4.77$ and

Table 1 Optimization of the reaction conditions based on the synthesis of **8a**



Entry	CuI (mol%)	Cat	Cat. (mol%)	Base	Solvent	t (h)	Yield (%)[a]
1	5	–	–	K_2CO_3	Toluene	24	0
2	5	**2**	5	K_2CO_3	Toluene	24	13
3	5	**4a**	5	K_2CO_3	Toluene	24	50
4	5	**4b**	5	K_2CO_3	Toluene	24	31
5	5	**4c**	5	K_2CO_3	Toluene	24	45
6	5	**4d**	5	K_2CO_3	Toluene	24	61
7	5	**4e**	5	K_2CO_3	Toluene	24	43
8	5	**4f**	5	K_2CO_3	Toluene	24	32
9	5	**4 g**	5	K_2CO_3	Toluene	24	24
10	–	**4d**	10	K_2CO_3	Toluene	24	-
10	5	**4d**	10	K_2CO_3	Toluene	24	62
11	5	**4d**	15	K_2CO_3	Toluene	24	62
12	10	**4d**	5	K_2CO_3	Toluene	24	61
13	**10**	**4d**	**10**	**K_2CO_3**	**Toluene**	**24**	**85**
14	10	**4d**	15	K_2CO_3	Toluene	24	85
15	15	**4d**	10	K_2CO_3	Toluene	24	85
16	10	**4d**	10	Cs_2CO_3	Toluene	24	63
17	10	**4d**	10	Et_3N	Toluene	24	55
18	10	**4d**	10	K_2CO_3	DMSO[b]	24	48
19	10	**4d**	10	K_2CO_3	DMF[b]	24	57
20	10	**4d**	10	K_2CO_3	Dioxane	24	52
21	10	**4d**	10	K_2CO_3	Toluene	12	47
22	10	**4d**	10	K_2CO_3	Toluene	18	64
23	10	**4d**	10	K_2CO_3	Toluene	30	85

[a]Reaction conditions: **5a** (1 mmol), **6a** (1.5 mmol), **7a** (1 mmol) and base (2 mmol), refluxed

[b]At 110 °C

4.36–4.30 ppm) on the eight-member ring shifted to the low field. Therefore, it can be speculated that the electron cloud density of eight-member ring, amide and triazole group in **4d** have changed. The possible reason is that the **4d** and Cu(I) formed a complex and the coordination cause the change of electron cloud density [38].

Several catalyst systems were also used to shed light on the reaction mechanism (Table 3).

From Table 3, CuI alone cannot promote the cascade reaction to give the intermediate product **I** or the target product **8a** (Table 3, Entry **1**), indicating that **4d** is

Table 2 Synthesis of **8** under optimum conditions

Entry[a]	Substrate **5**	Substrate **6**	Total yield (%)/t (h)	M.p. (°C)
8a	**5a**	**6a**	85/24[b]	286.5–287.8 (223–225 [18])
			76/48[c]	
			75/48[d]	
8b		**6b**	80/24[b]	176.0–177.8 (264–267 [18])
			71/48[c]	
			79/48[d]	
8c		**6c**	88/24[b]	186.5–188.4
8d	**5b**	**6a**	83/24[b]	241.5–243.1
8e		**6b**	79/24[b]	286.5–287.8
8f		**6c**	86/24[b]	193.1–194.9
8 g	**5c**	**6a**	86/24[b]	183.1–185.3
8 h		**6b**	81/24[b]	133.0–134.1
8i		**6c**	89/24[b]	219.4–221.3
8j	**5d**	**6a**	75/24[b]	214.7–216.2 (245–248 [18])
			56/30[c]	
			61/30[d]	
8 k		**6b**	70/24[b]	185.0–186.9 (190–193 [18])
			45/28[c]	
			49/28[d]	
8 l		**6c**	78/24[b]	137.6–139.2

[a]Reaction conditions: **5** (1 mmol), **6** (1.5 mmol), **7** (1 mmol), CuI (0.1 mmol), **4d** (0.1 mol), K_2CO_3 (2 mmol) and toluene (15 mL), refluxed in given time

[b]Total isolated yield (%)/total time (h) in this work

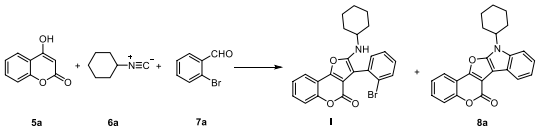
[c]Reported total yield (%)/total time (h) in two-step two-pot[18]

[d]Reported total yield (%)/total time (h) in two-step one-pot[18]

necessary whether as a catalyst in the first stage or as a ligand in the second stage. Without CuI, **4d** itself can only promote the first stage to afford **I** (Table 3, Entry **2**). Compound 4*H*-1,2,4-triazol-4-amine can also catalyze the first stage reaction to obtain **I**, but the yield is very low (28%, Table 3, Entry **3**), indicating that the synergy of TB skeleton and aminotriazole fragment works and the TB framework can increase the yield apparently.

Based on the results mentioned above and the literature [45], a possible mechanism was then proposed in Scheme 3. Firstly, the catalyst **4d** captured hydrogen atom of hydroxyl on **5a** to produce intermediate **A**. Then, intermediate **A** acted as nucleophile to attack **7a** to form intermediate **B**. Intermediate **C** was formed via dehydration of intermediate **B**. **6** attacked intermediate **C** as nucleophile to afford intermediate **D** after [4 + 1] cycloaddition. Then, the catalyst **4d-Cu** formed complex **I** with **D**, and the N atom in **I** reacted with Ar-Br by intramolecular addition

Table 3 Control experiments



Entry	Cat	CuI (mol%)	Yield of I (%)	Yield of 8a (%)
1	None	0	0	0
2	**4d**	0	73	0
3		0	28	0
4	None	10	0	0

Reaction conditions: **5** (1 mmol), **6** (1.5 mmol), **7** (1 mmol), catalyst (0.1 mol), CuI (0.1 mmol), K_2CO_3 (2 mmol) and toluene (15 mL), refluxed for 24 h

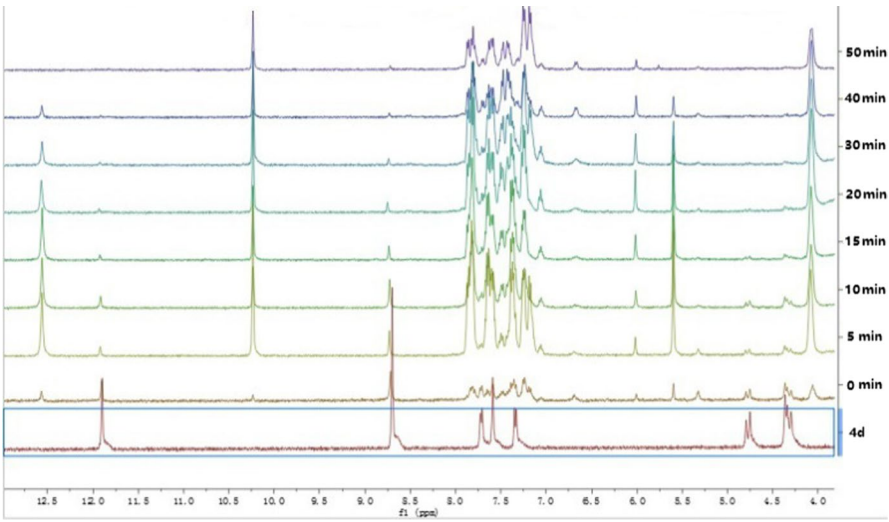
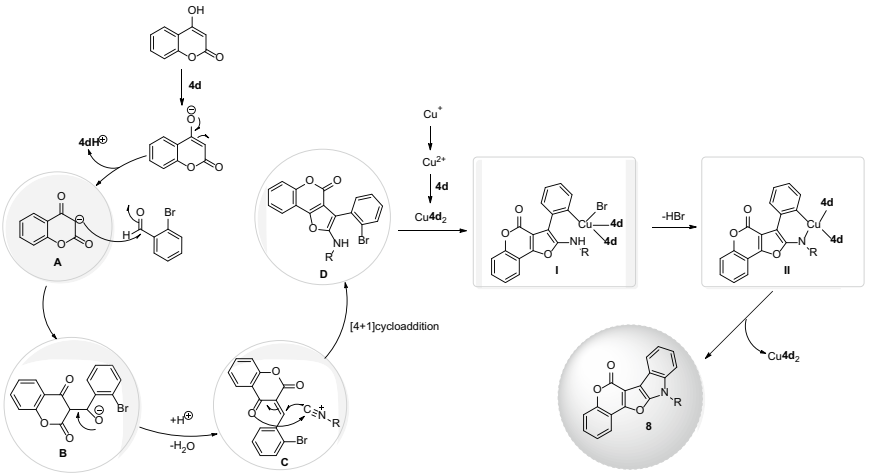


Fig. 2 The changes of the signals as the reaction proceeded (^{1}H NMR (400 MHz), DMSO-d_6)

to form intermediate **II**. The bromine atom in **II** was replaced by carbonate to form intermediate **III** and left in the form of bromine ion. The N–Cu interaction in **III** cleaved to form the final product **8**, and meanwhile, a carbonate was lost and the catalyst **4d-Cu** was recovered to complete a cycle.



Scheme 3 The possible reaction mechanism

Conclusion

In summary, a series of N^2,N^8-bis(nitrogen-containing heterocycle)-yl-2,8-dicarboxamide-Tröger's bases were synthesized. The most efficient **4d** was used to promote reaction of 4-hydroxycoumarin (or 2-hydroxy-1,4-naphoquinone), substituted benzaldehydes and isocyanide in mild condition. The results of catalysis mechanism investigation by ^{1}H NMR titration and control experiments showed the high catalytic efficacy of **4d** comes from its bifunction (the basic catalyst for the Aldol-[4 + 1]cycloaddition reaction and the ligand for the following copper-catalyzed intramolecular Ullmann reaction). Based on the high catalytic ability, the one-step one-pot preparation of the chromeno[3',4':4,5]furo[2,3-*b*]indoles and naphtho[2′,3′:4,5]furo[2,3-b]indoles was realized.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11164-022-04664-2.

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Declarations

Conflict of interest The authors declare no competing interests.

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