A Flexible Approach to the Chromenoquinolines under Copper/Lewis Acid Catalysis

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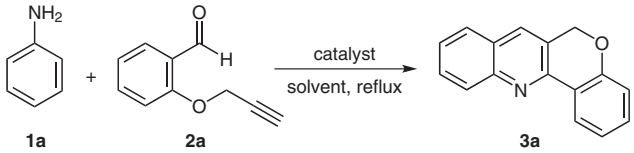
Abstract: The synthesis of chromenoquinolines via cyclization of different substituted anilines or naphthylamine with O-propargylated salicylaldehydes using CuI/La(OTf)$_3$ as an efficient catalyst in the reflux temperature of acetonitrile is reported.

Key words: chromenoquinoline, estrogenic agents, catalyst

There has been a considerable interest in the synthesis of quinolines and their derivatives as many naturally occurring quinolines are known for their interesting diverse applications.[1,2] Specially designed quinolines have been found in different fields including polymer science, pharmaceuticals, and agrochemicals. Some of the substituted chromenoquinolines that have been used as a drug that modulate the transcriptional activity of human progesterone receptor which play an important role in medicine and have been used therapeutically.[3] These kind of compounds have shown glucocorticoid receptor agonist, antagonist activity, and androgen receptor antagonist activity.[4] Particularly 6*H*-chromeno[4,3-*b*]quinolines have been used as an estrogenic agents. Estrogens can exert effects on tissues in several ways, and the most well-characterized mechanism of action is their interaction with estrogen receptors leading to alterations in gene transcription.[5] These are estrogen receptor modulators useful in the treatment of diseases such as osteoporosis, inflammatory bowel diseases, estrogen dependent cancers, anxiety disorders.[6] This anticipation led us to synthesis of 6*H*-chromeno[4,3-*b*]quinolines.

Only a few reports are available in the literature for the synthesis of 6*H*-chromeno[4,3-*b*]quinolines. These include the photochemical cyclization of chloro aryliminomethylbenzopyrans by Balasubramanian and coworkers,[7] intramolecular reaction of nitrilium salts,[8] thermal transformation of *N*-aryl-1-[4-(*N*-aryl)-amino-2*H*-chromen-3-yl]methylenimines,[9] and the reaction of β-chloroacrolin with 2-aminophenol.[10] In these reports longer reaction time was required, lower product yields were obtained, and harsh conditions were needed. Activation of a terminal alkyne C–H bond by transition-metal catalysts is one of the fundamental interests in organic synthesis. It has been reported that transition-metal catalysts such as Cu(I),[11] Au(I), Au(III), silver, and ruthenium can activate the terminal alkynes.[12] We chose copper catalyst[13] compared to other transition-metal catalysts since copper compounds are readily available, inexpensive, nontoxic catalyst, insensitive to air, and much cheaper than silver,[14] gold,[15] ruthenium, or other additives.[16]



Scheme 1 Synthesis of chromenoquinolines

Herein, we report the synthesis of 6*H*-chromeno[4,3-*b*]quinolines using the mixture of copper(I) iodide and lanthanum triflate as an efficient catalysts. Initially, we examined the reaction between aniline (**1a**) and O-propargylated salicylaldehyde **2a** as starting materials using different catalysts to optimize the reaction conditions (Scheme 1). It was found that 10 mol% of $BF_3{\cdot}OEt_2$ as a Lewis acid was not much useful to obtain the desired product and only 20% yield was obtained (Table 1, entry 1). Then we turned our attention to the use of other Lewis acids like $InCl_3$, La(OTf)$_3$ (entry 2 and 3) as catalysts for the synthesis of 6*H*-chromeno[4,3-*b*]quinoline because they are more reactive than $BF_3{\cdot}OEt_2$ in acetonitrile as solvent. Further optimization was performed to improve the yield of the product.

All Cu(I) species (entry 4–6) showed better catalytic properties. We could find out that catalytic property was excellent when we used Cu(I) species/Lewis acids or Brønsted acids combined (entries 7–14). When we employed AgOTf (entry 10) in combination with CuI, 76% of yield was obtained. On the other hand, only 60% of yield was obtained when we used CF_3COOH (entry 11) as a Brønsted acid. Transition-metal triflates such as scandium triflate, ytterbium triflate, and lanthanum triflate catalysts also furnished the reaction with good yields (entry 12–14). These three triflates have similar reactivity in terms of reaction yield. But we chose La(OTf)$_3$ for the further optimization of the reaction due to its low cost and stability under moisture. In particular, the combination of 10 mol% of each CuI and La(OTf)$_3$ (entry 14) gave the highest yield. We changed the mol percentage of the catalysts by 5 mol%, 10 mol%, and 20 mol% (entry 17 and 18). The use of 5 mol% of CuI/La(OTf)$_3$ gave 80% of yield which is lower than the reaction with 10 mol% of CuI/La(OTf)$_3$.

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Table 1 Optimization of Reaction Conditions

Entry	Catalyst	Solvent	Time (h)	Yield (%)[a]
1	$BF_3{\cdot}OEt_2$ (10 mol%)	MeCN	10	20
2	$La(OTf)_3$ (10 mol%)	MeCN	7	45
3	$InCl_3$ (10 mol%)	MeCN	8	40
4	CuBr (10 mol%)	MeCN	11	60
5	CuCl (10 mol%)	MeCN	7	65
6	CuI (10 mol%)	MeCN	5.5	70
7	CuBr/$La(OTf)_3$ (10 mol%)	MeCN	5.5	72
8	CuCl/$La(OTf)_3$ (10 mol%)	MeCN	6	75
9	CuI/$InCl_3$ (10 mol%)	MeCN	6	75
10	CuI/AgOTf (10 mol%)	MeCN	6	76
11	CuI/CF_3COOH (10 mol%)	MeCN	8	60
12	CuI/$Sc(OTf)_3$ (10 mol%)	MeCN	6	81
13	CuI/$Yb(OTf)_3$ (10 mol%)	MeCN	6	83
14	CuI/$La(OTf)_3$ (10 mol%)	MeCN	4	90
15	CuI/$La(OTf)_3$ (10 mol%)	THF	7	78
16	CuI/$La(OTf)_3$ (10 mol%)	DMF	8	82
17	CuI/$La(OTf)_3$ (10 mol%)	DMSO	8	74
18	CuI/$La(OTf)_3$ (10 mol%)	EtOH	10	67
19	CuI/$La(OTf)_3$ (20 mol%)	MeCN	4.5	89
20	CuI/$La(OTf)_3$ (5 mol%)	MeCN	4.5	80

[a] Yield refers to column purified product and 10 mol% of each CuI and $La(OTf)_3$ were calculated relative to the amines in all entries.

But 20 mol% of the catalyst did not change any considerable yield difference (entry 19).

Our further study has revealed that this cyclization reaction can be accelerated at an elevated temperature. When the reaction is run at reflux temperature of acetonitrile, 90% yield (entry 12) of desired product was obtained. Yield was less than 90% when other solvents like THF, DMF, DMSO, and EtOH (entry 13–16) were used. Finally, we found that synthesis of 6*H*-chromeno[4,3-*b*]quinoline in the presence of CuI/$La(OTf)_3$ (10 mol%) at reflux temperature of MeCN was good.

Having optimized the reaction conditions, a variety of amines **1a–i** were employed in this reaction and a range of 6*H*-chromeno[4,3-*b*]quinoline derivatives **3a–i** were synthesized (Scheme 2) in good yields. As evident from Table 2, all the amines with ring-activating groups in the *ortho*, *para*, and *meta* positions were participated in this reaction smoothly, and the yields of the products were remarkably similar. The single-crystal X-ray analysis of compound **3c** was also achieved in order to confirm their molecular structure (Figure 1).[17]

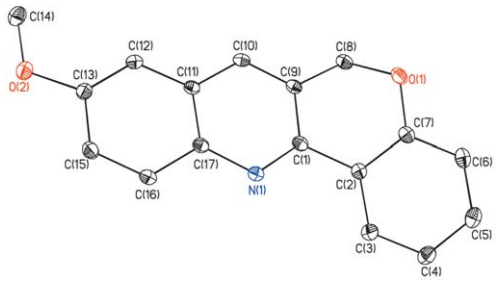
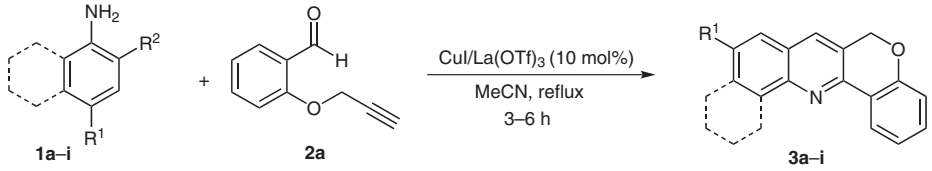


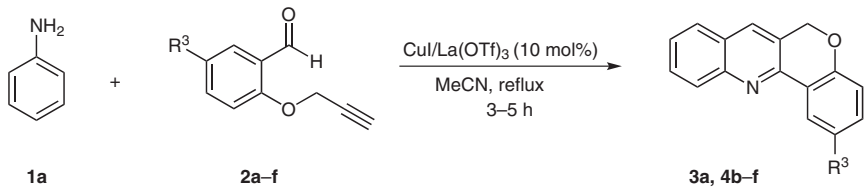
Figure 1 ORTEP diagram of **3c**

Ring-deactivating groups such as nitro-, carboxylate-, and nitrile-substituted anilines did not participate in the synthesis of chromenoquinolines. We tried the reaction with other heterocyclic amines like 4-aminopyridine, 2-methylquinolin-4-ylamine, and 1*H*-pyrrol-3-ylamine. But the reaction did not proceed with these amines. Naphthalen-1-ylamine **1i** gave 80% yield of the desired chromenoquinoline product **3i**. We reported the single-crystal X-ray analysis of the compounds **3b** and **3f** also.[17]

A series of O-propargylated salicylaldehydes **2a–f** were subjected to react with aniline (**1a**) by carrying out the reaction in the optimized conditions (Scheme 3). As shown in the Table 3, for most substrates the reaction pro-



Scheme 2 Synthesis of chromenoquinoline derivatives with different substituted anilines and naphthylamine **1a–i**



Scheme 3 Synthesis of chromenoquinoline derivatives with different substituted O-propargylated salicylaldehydes **3a**, **4b–f**

Table 2 Synthesis of Chromenoquinoline Derivatives with Different Substituted Anilines and Naphthylamine

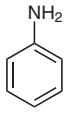
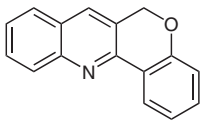
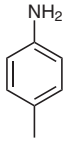
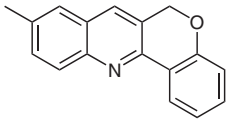
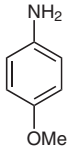
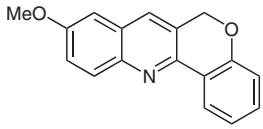
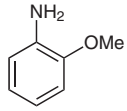
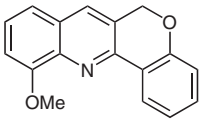
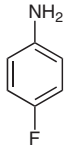
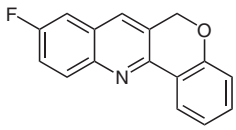
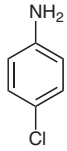
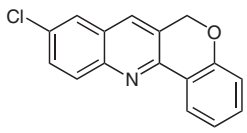
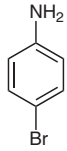
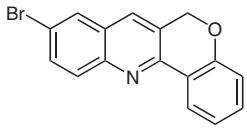
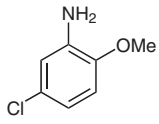
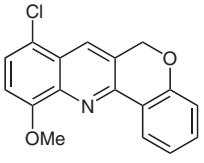
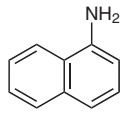
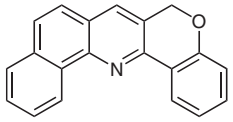
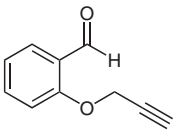
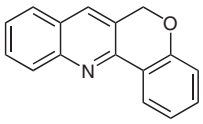
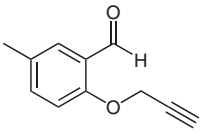
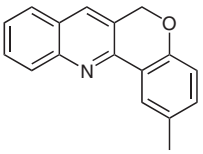
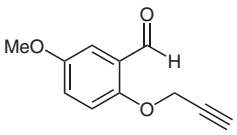
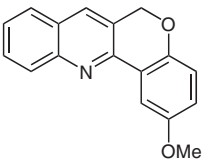
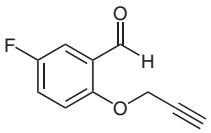
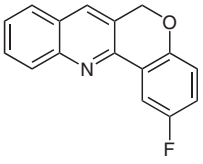
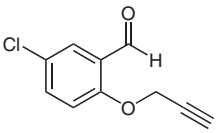
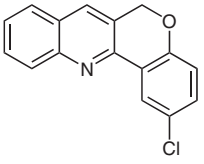
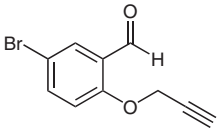
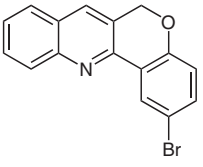
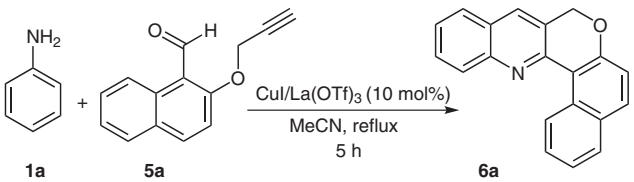
Entry	Amine	Product	Time (h)	Yield (%)
1	 **1a**	 **3a**	4.5	90
2	 **1b**	 **3b**	3	92
3	 **1c**	 **3c**	3.5	93
4	 **1d**	 **3d**	4	91
5	 **1e**	 **3e**	4	85
6	 **1f**	 **3f**	4	83
7	 **1g**	 **3g**	4.5	81
8	 **1h**	 **3h**	5.5	85
9	 **1i**	 **3i**	6	80

Table 3 Synthesis of Chromenoquinoline Derivatives with Different Substituted Aldehydes

Entry	Aldehyde	Product	Time (h)	Yield (%)
1	 **2a**	 **3a**	4.5	90
2	 **2b**	 **4b**	3.5	92
3	 **2c**	 **4c**	3	93
4	 **2d**	 **4d**	4	91
5	 **2e**	 **4e**	4	88
6	 **2f**	 **4f**	5	86

vided good yields of chromenoquinoline derivatives. It was noted that the substituents R^3 did not significantly affect the reaction.

To check the generality of this reaction, we used 2-*O*-propargyl-1-naphthaldehyde in this reaction (Scheme 4). The reaction proceeded well, and the product **6a** was obtained in 78% yield. ORTEP diagram of **6a** has been shown in Figure 2.[17]



Scheme 4 Synthesis of 8*H*-benzo[5,6]chromeno[4,3-*b*]quinoline

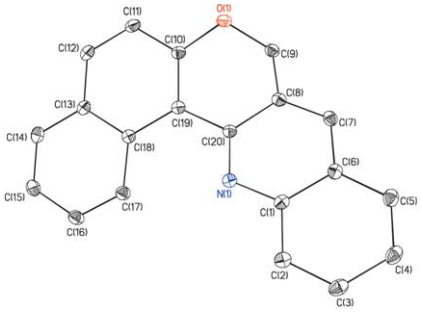


Figure 2 ORTEP diagram of **6a**

In summary, we described a novel and practical method for the synthesis of chromenoquinoline derivatives. In addition to its simplicity, this procedure has the advantage of high yields, easy availability and flexibility of starting materials, and short reaction times.[18]

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) The CCDC deposition number of **3c** is 753403; molecular formula: $C_{17}H_{13}NO_2$, chemical formula weight 263.28, monoclinic, unit cell parameters: a = 13.037 (8), b = 7.587 (4), c = 13.158 (8), β = 97.576 (9), space group P21/c.
The CCDC deposition number of **6a** is 753401; molecular formula: $C_{30}H_{13}NO$, chemical formula weight 283.31, monoclinic, unit cell parameters: a = 8.6729 (14), b = 15.418 (3), c = 10.8031 (18), β = 106.891 (2), space group P21/c.
The CCDC deposition number of **3b** is 753402; molecular formula: $C_{17}H_{13}NO$, chemical formula weight 247.29, monoclinic, unit cell parameters: a = 12.9795 (11), b = 23.1902 (19), c = 8.4440 (7), β = 95.2790 (10), space group P21/c.
The CCDC deposition number of **3f** is 753404; molecular formula: $C_{16}H_{10}ClNO$, chemical formula weight 267.71, monoclinic, unit cell parameters: a = 31.333 (3), b = 3.8586 (4), c = 40.188 (5), β = 102.334 (4), space group C2/c.
(18) **A Typical Procedure for the Preparation of 3a**
In a round-bottom flask equipped with a magnetic stirring bar, aniline (**1a**, 1.0 mmol), O-propargylated salicylaldehyde (**2a**, 1.0 mmol) in MeCN (20 mL), was added $La(OTf)_3$ (10 mol%) and CuI (10 mol%). Reaction mixture was stirred at reflux temperature of MeCN for 4 h. After completion of the reaction, as indicated by the TLC, the MeCN was evaporated and H_2O (20 mL) was added to the crude reaction mass. Then aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over anhyd Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (eluent: hexane–EtOAc) afforded **3a** (0.210 g, 90%); mp 126 °C. IR (KBr): 3051, 2295, 1649, 1033, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS): δ = 8.48 (1 H, d, J = 8.0 Hz), 8.11 (1 H, d, J = 8.0 Hz), 7.81 (1 H, s), 7.72 (1 H, d, J = 7.5 Hz), 7.67 (1 H, t, J = 7.5 Hz), 7.46 (1 H, t, J = 6.5 Hz), 7.36 (1 H, t, J = 7.5 Hz), 7.16 (1 H, t, J = 7.5 Hz), 7.01 (1 H, d, J = 7.5 Hz), 5.32 (2 H, s). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.4, 149.0, 148.3, 131.8, 130.9, 129.5, 129.4, 127.5, 127.4, 126.2, 125.5, 125.2, 123.2, 122.5, 117.3 (arom. C); 68.4 (aliph. C). MS (+): m/z = 234 [M + H]. Anal. Calcd for $C_{16}H_{11}NO$: C, 82.38; H, 4.75; N, 6.00. Found: C, 82.25; H, 4.80; N, 6.12.