Efficient One-Pot Synthesis of Substituted 4,7-Phenanthroline, Pyrano-[3,2-*f*]quinoline and Pyrano[3,2-*g*]quinoline Derivatives by Aza-Diels–Alder Reaction

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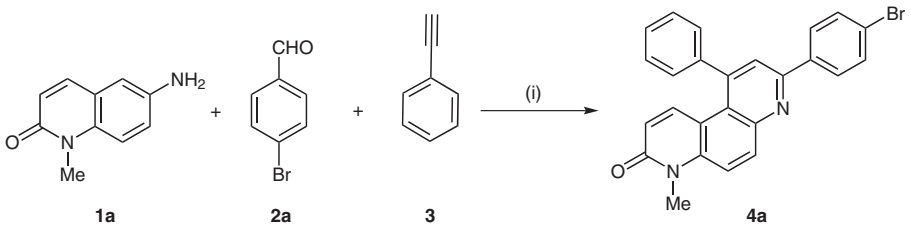
Abstract: A mild and efficient method for the synthesis of pyrano[3,2-*f*]quinoline and 4,7-phenanthroline derivatives via three-component domino reaction of heterocyclic amines, aldehydes, and terminal alkyne using $BF_3{\cdot}OEt_2$ as Lewis acid catalyst is described. The features of this procedure are mild reaction conditions, good to high yields, and operational simplicity.

Key words: multicomponent reaction, $BF_3{\cdot}OEt_2$, 4,7-phenanthroline, pyrano[3,2-*f*]quinoline, pyrano[3,2-*g*]quinoline, aromatic aldehyde, phenyl acetylene

Multicomponent reactions (MCR) have attracted considerable attention in combinatorial and medicinal chemistry and have been designed to produce elaborate biologically active compounds.[1] Multicomponent reactions are convergent reactions, in which three or more starting materials react to give a highly complex product in one pot. The multistep synthesis of a complex compound is laborious and tedious, generating several equivalents of waste, salt and byproducts.[2] Whereas multicomponent reaction generally occurs in one pot and exhibits high atom economy and selectivity and thus MCRs are advantageous compared to linear stepwise synthesis by reducing reaction time, saving money and raw materials. Multicomponent reactions involving the simultaneous molecular interactions of three or more components, selectivity is a particular concern because different products can be formed in the reaction pathway.[3] Moreover MCR are an ideal synthetic tool for generating multiple molecular scaffolds and to increase structural and skeletal diversity.

The heterocyclic system quinoline represent an important class of alkaloids and are often found as structural frameworks in a large number of biologically active natural products and pharmaceuticals.[4] Quinoline nucleus has found broad application in drug development for the treatment of melanin concentrating hormone (MCH)-receptor-related disorder,[5] cell proliferative diseases,[6] transmissible spongiform encephalopatheies,[7] malignant tumor, such as stomach cancer, brain tumor, and large instetine cancer,[8] and bacterial infections in mammals.[9] They also find application in material science,[10] bioorganometallic processes,[11] and agrochemicals and effect chemicals such as dyestuffs and corrosion inhibitors.[12] Moreover substituted quinolines show numerous biological activity as antagonists of endothelin,[13] $5HT_3$,[14] and NK-3 receptors[15] and also function as inhibitors of gartric (H^+/K^+)-ATPase[16] and dihydroorotate dehydrogenase.[17] Moreover, it is expected that pyrano[3,2-*f*] quinoline, which contain both a quinoline ring and pyran moieties, afford unique biological activities, such as psychotropic activity,[18] antiallergic activity,[19] anti-inflammatory activity,[20] estrogenic activity,[21] and are used as potential pharmaceuticals.[22] Helietidine, dutadrupine, and geibalansine[23] are examples of natural products containing pyranoquinoline core structure. 4,7-Phenanthroline derivatives and its analogues exhibit a high antibacterial activity and are used for treatment of gastrointestinal disease.[24–29]

In view of the importance of pyrano quinoline and its derivatives, several methods were developed for the synthesis of pyrano quinoline by aza-Diels–Alder reaction.[30] However, many of these synthetic protocols reported so far suffer from disadvantages, such as harsh reaction conditions, multistep reaction, expensive reagents and longer reaction time, large amount of catalyst and lower yields. Therefore, a new protocol with reagent economy, one-pot reaction, cheaper catalyst, and improved yields is desir-



1a 2a 3 4a

Scheme 1 *Reagents and conditions*: (i) $BF_3{\cdot}OEt_2$, toluene, reflux, 4 h.

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able. In continuation of our work on the synthesis of quinoline-annulated heterocyclic compounds[31] we became interested to develop a methodology for the synthesis of pyrano[3,2-*f*]quinoline and phenanthroline derivatives. Herein, we present our recent investigation.

Treatment of the aromatic aldehyde, 6-amino coumarin or 6-amino quinolone, and phenyl acetylene in the presence of 10 mol% of $BF_3{\cdot}OEt_2$ in toluene at reflux conditions afforded the corresponding pyrano quinoline derivatives or phenanthroline derivatives in high yields (Scheme 1). In our initial study the reaction of *N*-methyl 6-amino quinolone (**1**), 4-bromo benzaldehyde (**2**), and phenyl acetylene (**3**) were used as a model reaction to optimize the reaction conditions, and the results are presented in Table 1.

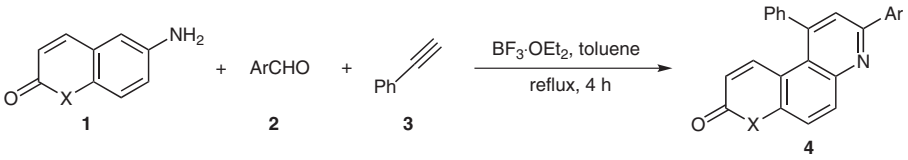
To obtain maximum yield of the product a small excess of the amine and aromatic aldehyde with respect to phenyl acetylene was required: 1.1 equivalents of both amine and aldehyde with respect to phenyl acetylene is sufficient to bring about the improved yield. Further increase in molar amounts resulted in side reactions. Having established the optimized reaction conditions various aldehydes (**2a–i**) were subjected to undergo the reaction with various heterocyclic amines (**1a–d**) to give the substituted quinolines (**4a–n**) in high yields within few hours (Table 2). It is observed that both electron-donating and electron-withdrawing substituents on the aromatic aldehydes and heterocyclic aldehydes gave the desired quinolines in high yields. The *ortho*, *meta*, and *para* substituents on the aromatic ring of the aldehydes gave almost similar yields. Reactions with alkynes like *n*-hexyne and *n*-heptyne did not give the desired products. Besides, aliphatic aldehydes like formaldehyde and acetaldehyde did not undergo such reaction. A variety of substituted heterocyclic amines were reacted with various aldehydes and phenyl acetylene, and in all the cases the desired products were obtained in good yields. These multicomponent reactions with excellent selectivity inspired us to react 4-methoxybenzaldehyde (**2c**), phenyl acetylene (**3**) with 4-methyl-7-aminocoumarin (**1d**). However, the expected cyclized product **4n** was obtained in only 53% yield. Perhaps this lower yield is due to the less reactivity of 4-methyl-7-aminocoumarin (**1d**) than that of the other amines (**1a–c**).

Table 1 Synthesis of Pyrano[3,2-*f*]quinoline and Phenanthroline Derivatives under Various Experimental Conditions

Entry	Temp (°C)	Acid catalyst (mol%)[a]	Solvent	Time (h)	Yield (%)[b]
1	r.t.	–	toluene	24	0
2	reflux	–	toluene	24	0
3	r.t.	$BF_3{\cdot}OEt_2$ (10)	toluene	24	0
4[c]	reflux	$BF_3{\cdot}OEt_2$ (10)	toluene	4	87
5	reflux	$Yb(OTf)_3$ (10)	toluene	4	61
6	reflux	CuBr (10)	toluene	6	35
7	reflux	CuI (10)	toluene	6	48
8	reflux	TFA (10)	toluene	4	55
9	reflux	PTSA (10)	toluene	4	51
10	reflux	$BF_3{\cdot}OEt_2$ (10)	MeCN	4	72
11	reflux	$BF_3{\cdot}OEt_2$ (10)	THF	4	69
12	reflux	$BF_3{\cdot}OEt_2$ (10)	DMF	4	75
13	reflux	$BF_3{\cdot}OEt_2$ (10)	EtOH	4	61
14	reflux	$BF_3{\cdot}OEt_2$ (20)	toluene	4	84
15	reflux	$BF_3{\cdot}OEt_2$ (5)	toluene	4	81

[a] Conditions: mol% of acid catalyst required relative to the phenyl acetylene in all the entries.
[b] Isolated yields.
[c] Optimized reaction conditions.

Table 2 Synthesis of Various Substituted Pyrano Coumarin and Phenanthroline Derivatives



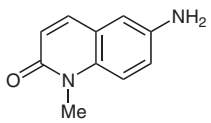
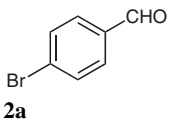
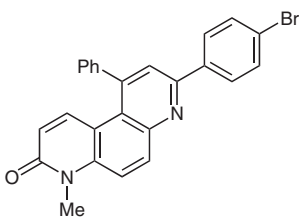
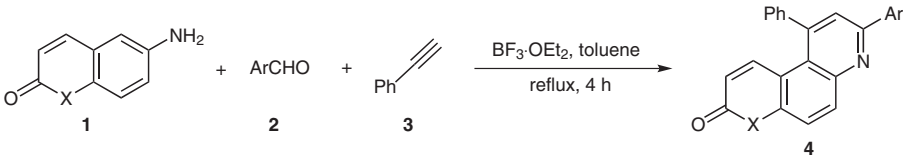
Entry	Amines **1a–d**	Aldehydes **2a–j**	Products **4a–n**	Yield (%)[a]
1	 **1a**	 **2a**	 **4a**[32]	87

Table 2 Synthesis of Various Substituted Pyrano Coumarin and Phenanthroline Derivatives (continued)



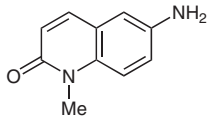
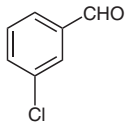
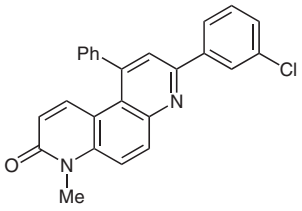
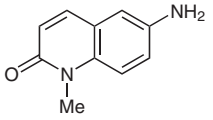
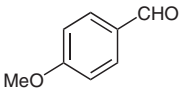
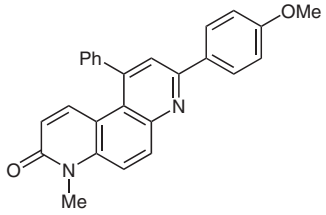
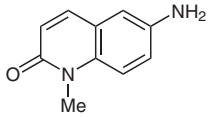
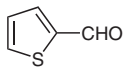
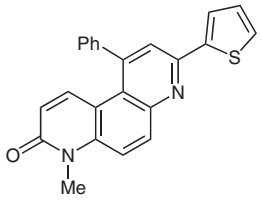
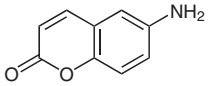
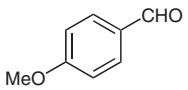
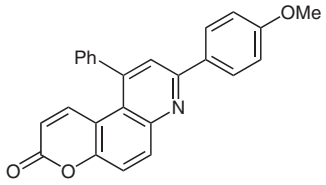
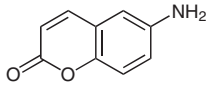
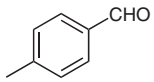
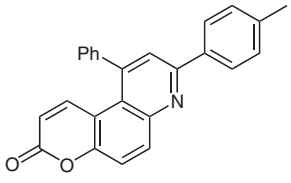
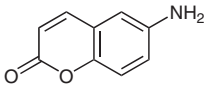
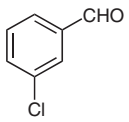
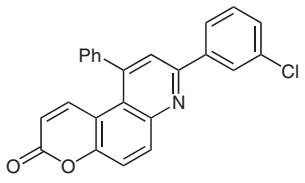
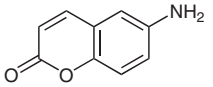
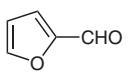
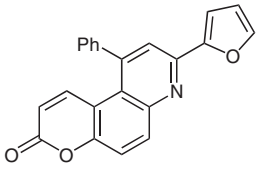
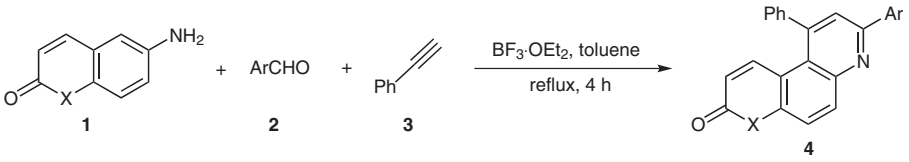
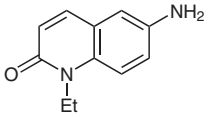
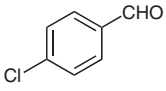
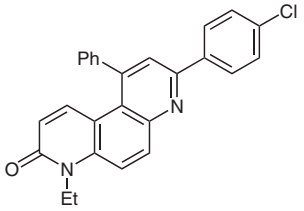
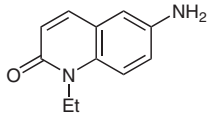
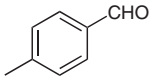
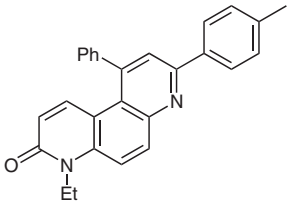
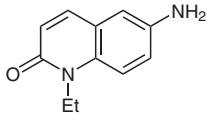
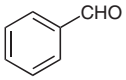
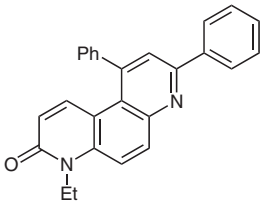
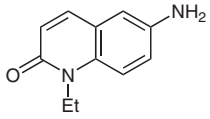
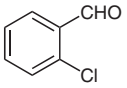
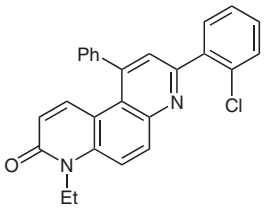
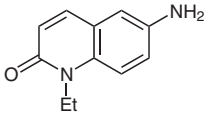
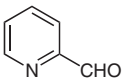
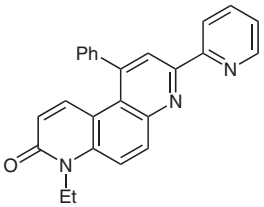
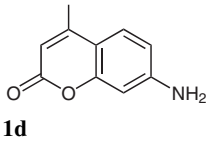
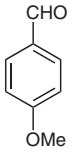
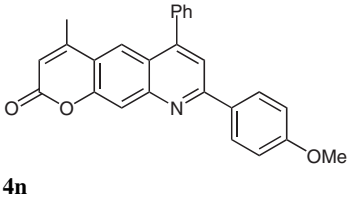
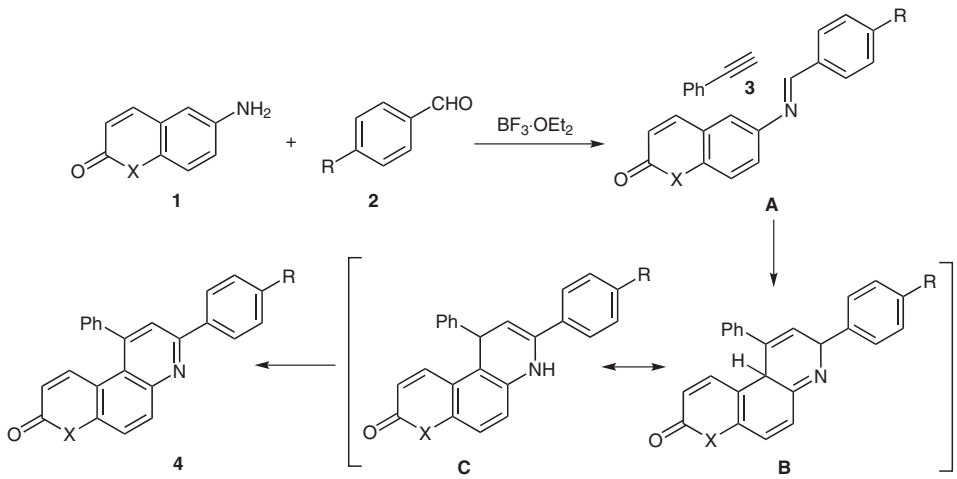
Entry	Amines **1a–d**	Aldehydes **2a–j**	Products **4a–n**	Yield (%)[a]
2	 **1a**	 **2b**	 **4b**	81
3	 **1a**	 **2c**	 **4c**	83
4	 **1b**	 **2d**	 **4d**	80
5	 **1b**	 **2c**	 **4e**	86
6	 **1b**	 **2e**	 **4f**	84
7	 **1b**	 **2b**	 **4g**	81
8	 **1b**	 **2f**	 **4h**	79

Table 2 Synthesis of Various Substituted Pyrano Coumarin and Phenanthroline Derivatives (continued)



Entry	Amines **1a–d**	Aldehydes **2a–j**	Products **4a–n**	Yield (%)[a]
9	 **1c**	 **2g**	 **4i**	83
10	 **1c**	 **2e**	 **4j**	79
11	 **1c**	 **2h**	 **4k**	77
12	 **1c**	 **2i**	 **4l**	77
13	 **1c**	 **2j**	 **4m**	74
14	 **1d**	 **2c**	 **4n**	53

[a] Isolated yields.



Scheme 2 The proposed mechanism for the synthesis of pyrano quinoline and phenanthroline derivatives

The reaction was first carried out in toluene without any catalyst at room temperature and refluxing conditions. It was found that no product was formed without any catalyst (Table 1, entries 1 and 2). Similar reaction was attempted in the presence of 5 mol%, 10 mol%, 20 mol% of $BF_3{\cdot}OEt_2$ (entries 4, 14, 15) and found that the reaction was completed at 10 mol% $BF_3{\cdot}OEt_2$ at reflux in toluene for four hours (entry 4). Lower or higher loading of the catalyst had no significant effect on the reaction yield. To find the optimum reaction conditions we used several Lewis and Brønsted acids under the same reaction conditions (entries 5–9). $BF_3{\cdot}OEt_2$ gives better yield compared to other Lewis acids. Brønsted acids give much lower yield compared to $BF_3{\cdot}OEt_2$. In addition, MeCN, THF, DMF, EtOH (entries 10–13) were also tested as solvents. In these cases product **4a** was formed in lower yield. Variation of the catalyst and solvent showed that running the reaction in refluxing toluene using 10 mol% $BF_3{\cdot}OEt_2$ provides the best result.

Plausible rationalization for the formation of pyrano[3,2-*f*]quinoline and phenanthroline derivatives is outlined in Scheme 2. Initially, a BF_3-catalyzed imine **A** is formed which possess the aza-heterodiene moiety. This undergoes intermolecular aza-Diels–Alder reaction with the alkyne which is activated by $BF_3{\cdot}OEt_2$ to give the products **4** via B↔C.

Chiral Lewis acid or chiral Brønsted acid catalyzed large number of asymmetric aza-hetero Diels–Alder reactions are well known where active preformed diene are used as reaction component.[33–38] The direct asymmetric aza-hetero Diels–Alder reaction of alkynes which avoids the use of preformed dienes, has been less extensively studied.[39] Very recently Kulkarni and Török reported microwave-assisted multicomponent domino cyclization–aromatization for the synthesis of substituted quinolines.[40] Gaddam and co-workers reported CuI/$La(OTf)_3$-catalyzed, one-pot synthesis of isomeric ellipticine derivatives in ionic liquids.[41] However, there is no report of the synthesis of pyrano[3,2-*f*]quinoline, pyrano[3,2-*g*]quinoline, or phenanthroline derivatives avoiding preformed dienes by multicomponent domino reaction of heterocyclic amines, aromatic aldehydes, and unactivated alkyne in one pot. According to our knowledge this is the first example of multicomponent aza-Diels–Alder reaction of unactivated alkynes with any heterocyclic amines in the absence of any copper catalyst under conventional heating avoiding microwave irradiation.

In conclusion we have demonstrated a novel, mild, and efficient strategy for the synthesis of potentially biologically active pyrano[3,2-*f*]quinoline, pyrano[3,2-*g*]quinoline, or phenanthroline derivatives by multicomponent aza-Diels–Alder reaction of various heterocyclic amines, aldehydes, and unactivated alkyne. The methodology is simple, rapid, and inexpensive affording good to high yields with operational simplicity.

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

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(32) **Synthesis of Compound 4a**

A mixture of the heterocyclic amine **1a** (0.287 mmol) and aromatic aldehyde **2a** (0.287 mmol) was stirred in toluene at r.t. for 10 min. After addition of 10 mol% $BF_3{\cdot}OEt_2$ (mol% calcd relative to the phenyl acetylene **3**) phenyl acetylene (**3**, 0.261 mmol) was added, and the reaction mixture was refluxed for 4 h. After completion of the reaction as monitored by TLC the reaction mixture was cooled and diluted with sat. $NaHCO_3$ solution (40 mL). This was extracted with EtOAc (3 × 20 mL). The combined organic extract was washed with brine and dried over Na_2SO_4. The solvent was distilled off. The resulting crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc (4:1) as eluent to give the compound **4a**. Yield 87%; colorless solid; mp 270–272 °C. IR (KBr): 1123, 1475, 1543, 1668, 2949 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3 H), 6.36 (d, *J* = 10.0 Hz, 1 H), 7.43 (q, *J* = 2.7 Hz, 2 H), 7.50 (d, *J* = 10.0 Hz, 1 H), 7.54–7.55 (m, 3 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 7.78 (s, 1 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 2 H), 8.38 (d, *J* = 9.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4, 114.8, 118.8, 119.0, 122.5, 123.1, 124.1, 128.3, 128.7, 128.8, 129.4, 132.0, 133.8, 137.1, 137.4, 140.4, 141.7, 145.7, 148.1, 154.1, 161.7. MS: *m/z* = 441, 443 $[M + H]^+$. Anal. Calcd (%) for $C_{25}H_{17}BrN_2O$: C, 68.04; H, 3.88; N, 6.35. Found: C, 67.82; H, 3.67; N, 6.37.

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