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Synthesis of substituted quinolines from *N*-aryl-*N*-(2-alkynyl)toluenesulfonamides via $FeCl_3$-mediated intramolecular cyclization and concomitant detosylation

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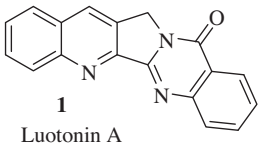
ABSTRACT

A series of substituted quinolines have been synthesized in moderate to good yields (55–81%) from easily available substrates *N*-aryl-*N*-(2-alkynyl)toluenesulfonamides via $FeCl_3$-mediated intramolecular cyclization and concomitant detosylation.

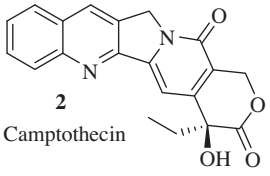
The quinoline nucleus is found in many naturally occurring compounds with remarkable biological activities.[1] Luotonin A (**1**) a pyrroloquinazolinoquinoline alkaloid extracted from the Chinese medicinal plant *Peganum nigellastrum*[2] acts as a cytotoxic agent toward murine leukemia P-388 cell line (IC_{50} 1.8 μg/mL). Camptothecin (**2**) is also an alkaloid, isolated from the bark and stem of *Camptotheca acuminata* (Camptotheca, Happy tree), a tree native to China used as an anticancer agent in traditional Chinese medicine[3] (Fig. 1).

Moreover, members of this family possess antimalarial,[4] antiinflammatory,[5] antiasthmatic,[6] antibacterial,[7] antihypertensive,[8] and tyrosine kinase inhibiting[9] activities. Besides, quinolines are valuable synthons for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic, or non-linear optical properties with excellent mechanical properties.[10]

In view of the broad array of biological activity, several methods for the construction of this heterocyclic nucleus have been reported. Although methods such as the Skraup,[11] Döebner-von Miller,[12] Friedländer,[13] and Combes[14] procedures have been reported in the literature, the Friedländer annulations are the most straightforward method to produce polysubstituted quinolines. The reaction involves an acid or a base catalyzed annulation reaction between 2-aminoaryl ketone and a carbonyl compound possessing a reactive α-methylene group. Classically, the Friedländer reaction is carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base or by heating at high temperatures ranging from 150–220 °C in the absence of any catalyst.[15] Subsequent work showed that acid catalysts are more effective than base catalysts.[16] Several acid catalysts have been used in the Friedländer annulations *viz*. Bronsted acids like sulfamic acid, hydrochloric acid, sulfuric acid, *p*-toluene sulfonic acid, phosphoric acid etc[16] and Lewis acids such as $FeCl_3$ or $Mg(ClO_4)_2$,[17] $SnCl_2$–$ZnCl_2$,[18] $SnCl_2{\cdot}2H_2O$,[19] $Bi(OTf)_3$,[20] $Yb(OTf)_3$,[21] $Ag_3PW_{12}O_{40}$,[22] and $NaAuCl_4{\cdot}2H_2O$[23] have been reported to be effective for the synthesis of quinoline. Besides, there are also several methods reported for the synthesis of quinolines using various types of catalysts, for example, molecular-iodine,[24] $In(OTf)_3$,[25] CAN,[26] $RuCl_2(PPh_3)_3$,[27] $[RhCp^*Cl_2]_2$[28] etc. Moreover, substituted quinolines have also been synthesized by the Baylis–Hillman reaction[29] as well as Photo-Fries rearrangement.[30] However, many of these procedures suffer from harsh reaction conditions,[27] longer reaction time,[23] difficulties in work-up,[19] and the use of relatively expensive reagents.[21–23,25,27,28]



1
Luotonin A



2
Camptothecin

Figure 1. Naturally occurring biologically active quinoline alkaloids.

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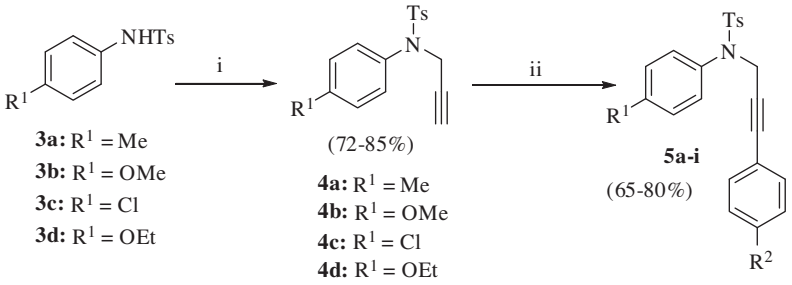
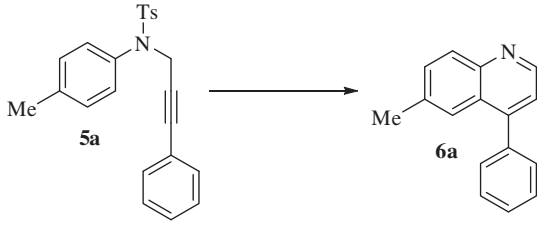


Reagents and conditions: (i) Propargyl bromide (1.5 equiv), anhydrous K_2CO_3 (4.0 equiv), dry acetone, reflux, 6-8 h; (ii) substituted iodobenzene (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (3 mol%), DMF-Et_3N (4:1), r.t., 0.5-1.0 h.

Scheme 1. Synthesis of *N*-aryl-*N*-(2-alkylnyl)toluenesulfonamides.

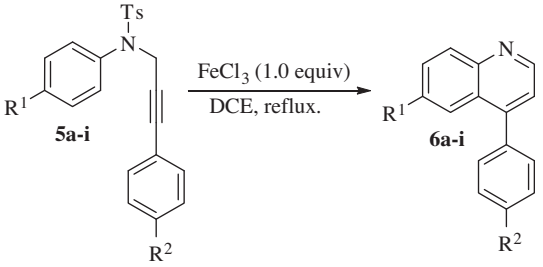
Table 1
Optimization of reaction conditions for synthesis of **6a**



Entry	Catalyst (equiv)	Solvent/*T* (°C)	Time (h)	Yield[a] (%)
1	$FeCl_3$ (0.2)	DCE/reflux	2	15
2	$FeCl_3$ (0.5)	DCE/reflux	2	35
3[b]	$FeCl_3$ (1.0)	DCE/reflux	1	70
4	$FeCl_3$ (1.5)	DCE/reflux	1	70
5[c]	$FeCl_3$ (1.0)	DCE/reflux	1	69
6	$FeCl_3$ (1.0)	DCE/25	12	n.r.
7	$FeCl_3$ (1.0)	CH_3CN/reflux	2	50
8	$FeCl_3$ (1.0)	EtOH/reflux	8	45
9	$FeCl_3$ (1.0)	$CHCl_3$/reflux	1.5	68
10	$FeCl_3$ (1.0)	CH_2Cl_2/reflux	2.5	52
11	$FeCl_3$ (1.0)	CH_3NO_2/100	2	35
12	$FeCl_3$ (1.0)	Toluene/100	3	17
13	$FeCl_3$ (1.0)	Dioxane/100	3	22
14	$FeCl_3 \cdot 6H_2O$ (1.0)	DCE/reflux	2	10
15	$Fe(NO_3)_3$ (1.0)	DCE/reflux	3	Trace
16	$Fe_2(SO_4)_3$ (1.0)	DCE/reflux	3	Trace

[a] Isolated yield of the product.
[b] Optimized reaction condition.
[c] Reaction was carried out in nitrogen atmosphere, n.r. = no reaction.

Table 2
Synthesis of substituted quinolines



Entry	Substrate	R^1	R^2	Product	Time (h)	Yield[a] (%)
1	**5a**	Me	H	**6a**	1.0	70
2	**5b**	Me	OMe	**6b**	0.5	75
3	**5c**	Me	CO_2Me	**6c**	7.0	58
4	**5d**	OMe	OMe	**6d**	0.5	81
5	**5e**	OMe	COMe	**6e**	9.0	55
6	**5f**	Cl	OMe	**6f**	0.5	72
7	**5g**	Cl	CO_2Me	**6g**	8.0	56
8	**5h**	Cl	OEt	**6h**	0.5	78
9	**5i**	OEt	OMe	**6i**	0.5	80

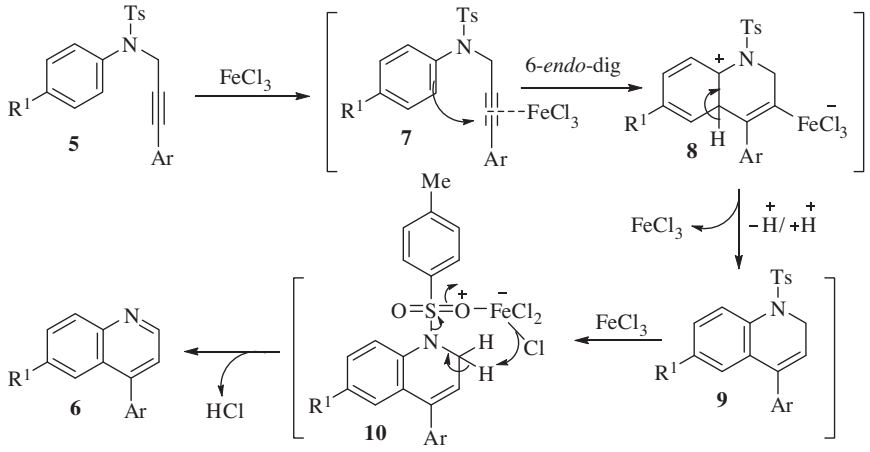
[a] Isolated yield of the product.

In recent years, the development of sustainable, environmentally friendly, and low cost C–C and C–X bond forming protocols have attracted much attention in synthetic organic chemistry. Many excellent works concerning direct C–C and C–X bond forming reactions catalyzed or mediated by iron have been reported.[31] In one report, Takaki et al.[31j] have used $Fe(OTf)_3$ for the cyclization of aryl-substituted alkynes to obtain 1,2-dihydroquinolines. But by changing the catalyst $Fe(OTf)_3$ to $FeCl_3$ interestingly we have achieved the synthesis of quinoline derivatives. Herein, we report our results.

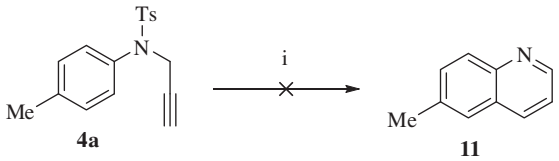
The starting precursors, *N*-aryl-*N*-(2-alkynyl)toluenesulfonamides **5a–i** were prepared in 65–80% yields from **4a–d** via Sonogashira coupling reaction with substituted iodobenzene. Compounds **4a–d** were in turn synthesized in 72–85% yields from **3a–d** by the reaction with propargyl bromide in the presence of anhydrous K_2CO_3 in refluxing acetone for 6–8 h (Scheme 1).

We initiated our investigation with substrate **5a**[32] and the results are summarized in Table 1. When substrate **5a** was subjected to react with $FeCl_3$ (0.2 equiv) in 1,2–dichloroethane (DCE) under reflux for 2 h, the quinoline derivative **6a**[33] was obtained in only 15% yield (Table 1, entry 1). By increasing the amount of $FeCl_3$ up to 1.0 equiv, the yield of the quinoline derivative **6a** was increased (Table 1, entries 2 and 3). Further increase in the amount of $FeCl_3$ did not improve the yield of product **6a** (Table 1, entry 4). The reaction under nitrogen atmosphere also gave similar results (Table 1, entry 5). But at 25 °C temperature any trace amount of the desired quinoline derivative **6a** was not obtained, instead the starting material **5a** was recovered unchanged (Table 1, entry 6). Next the effect of solvent on the yield of quinoline derivative **6a** was studied. Use of CH_3CN, EtOH, $CHCl_3$, CH_2Cl_2, CH_3NO_2, toluene, and dioxane as solvents led to lower yields of the desired product **6a** (Table 1, entries 7–13). Other iron-catalysts viz. $FeCl_3 \cdot 6H_2O$, $Fe(NO_3)_3$, and $Fe_2(SO_4)_3$ were also used for testing their effectiveness toward the formation of quinoline **6a**, but these were found to be less effective for the reaction (Table 1, entries 14–16). It became apparent that the optimized reaction condition is the use of 1.0 equiv of $FeCl_3$ in DCE under reflux which provides the best result (Table 1, entry 3).

To test the generality of the reaction, the other substrates **5b–i** were treated under optimized reaction condition and the substituted quinolines **6b–i** were obtained in 55–81% yields (Table 2). From Table 2 it is seen that the substrates having electron-donating



Scheme 2. A proposed mechanism for the $FeCl_3$-mediated cyclization of *N*-aryl-*N*-(2-alkylnyl)toluenesulfonamides.



Reagents and conditions : (i) $FeCl_3$ (1.0 equiv), DCE, reflux, 8 h.

Scheme 3. $FeCl_3$-mediated reaction of *N*-propargyl aniline **4a**.

groups like OMe and OEt present in the benzene ring of the terminal acetylenic part gave higher yields of the products and in a relatively shorter reaction time, whereas substrates with electron-withdrawing groups like CO_2Me and COMe gave lower yields and required longer reaction time.

The structure of quinoline derivatives **6** was determined from their analytical and spectral data. A proposed reaction mechanism for the $FeCl_3$-mediated cyclization of *N*-aryl-*N*-(2-alkynyl)toluenesulfonamides is depicted in Scheme 2. Initially the alkyne moiety of **5** is activated by $FeCl_3$ to generate π-complexes **7**, which by subsequent intramolecular 6-*endo*-dig mode of cyclization may produce the charged species **8** which on simultaneous deprotonation-protonation followed by loss of $FeCl_3$ (protodemetalation) produced the intermediates **9**. Finally detosylation-aromatization of the intermediates **9** via the formation of **10** may afford the corresponding quinoline derivatives **6**. Notably we have been successful to isolate only the intermediate **9d**[34] by using shorter reaction time (15 min.). This intermediate **9d** on further reaction with $FeCl_3$ in DCE under reflux gave the quinoline derivative **6d**.

When substrate **4a**, having monosubstituted alkyne moiety was subjected to react with $FeCl_3$ under optimized reaction condition, the desired quinoline derivative **11** was not obtained instead the starting material was recovered unchanged (Scheme 3). This may be due to the absence of a benzene ring at the terminal alkyne moiety of substrate **4a** and therefore, it was unable to produce the π-complex **7** (Scheme 2) by $FeCl_3$. It is relevant to mention here that the synthesis of substituted quinolines has earlier been reported via two-component[17] and three-component[31m] reactions using $FeCl_3$ in ethanol and toluene at room temperature and 110 °C respectively.

In conclusion, we have successfully developed an inexpensive and efficient method for the synthesis of substituted quinolines in moderate to good yields from easily available starting materials *N*-aryl-*N*-(2-alkynyl)toluenesulfonamides via $FeCl_3$-mediated intramolecular cyclization. This process can provide a diverse range of quinoline derivatives from simple starting materials. The procedure is simple and detosylation occurs under the reaction condition.

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32. *Typical procedure for the synthesis of compound* ***5a***: To a stirred solution of compound **4a** (500 mg, 1.67 mmol), iodobenzene (408 mg, 2.00 mmol) and dry Et_3N (2 mL), in dry DMF (8 mL) catalysts, $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol) and CuI (10 mg, 0.05 mmol) were added and the reaction mixture was stirred at room temperature for 1 h. After completion, the reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was successively washed with water (5 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude mass which was chromatographed over silica gel (60–120 mesh) using ethyl acetate-petroleum ether (1:9) as eluent to afford the product **5a** as a white solid. Yield: 65%; mp 74–76 °C; IR (KBr): ν_{max} = 1163, 2246, 2919, 3055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.63 (s, 2H, NCH_2), 7.12 (d, *J* = 8.0 Hz, 2H, ArH), 7.18–7.20 (m, 6H, ArH), 7.27–7.31 (m, 3H, ArH), 7.60 (d, *J* = 8.0 Hz, 2H, ArH) ppm; MS (ESI): *m*/*z* = 398 $[M+Na]^+$; Anal. Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73%. Found: C, 73.43; H, 5.65; N, 3.70%.
33. *Typical procedure for the synthesis of quinoline derivative* ***6a***: To a stirred solution of compound **5a** (150 mg, 0.39 mmol) in 1,2-dichloroethane (5 mL), $FeCl_3$ (63 mg, 0.39 mmol) was added. The reaction mixture was then refluxed for 1 h and cooled to room temperature. CH_2Cl_2 (50 mL) was added and the organic layer was successively washed with water (2 × 20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude mass which was flash chromatographed over silica gel (230–400 mesh) using ethyl acetate-petroleum ether (3:17) as eluent to afford the quinoline derivative **6a** as a colorless gummy mass. Yield: 70%; IR (KBr): ν_{max} = 1583, 2917, 3057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 2.45 (s, 3H, CH_3), 7.27 (d, *J* = 4.4 Hz, 1H, ArH), 7.48–7.56 (m, 6H, ArH), 7.65 (s, 1H, ArH), 8.07 (d, *J* = 8.4 Hz, 1H, ArH), 8.86 (d, *J* = 4.4 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.8, 121.4, 124.5, 126.7, 128.3, 128.6, 129.5, 131.6, 136.5, 138.2, 147.3, 147.8, 149.0 ppm; HRMS (ESI): Calcd for $C_{16}H_{13}NNa$ $[M+Na]^+$ 242.0946. Found: 242.0961.
34. *6-Methoxy-4-(4-methoxyphenyl)-1-tosyl-1,2-dihydroquinoline (****9d****)*: Yield: 15%; white solid, mp 118–120 °C; IR (KBr): ν_{max} = 1158, 2932, 3037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 2.27 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.47 (d, *J* = 4.0 Hz, 2H, NCH_2), 5.52 (t, *J* = 4.4 Hz, 1H, =CH), 6.41 (d, *J* = 2.4 Hz, 1H, ArH), 6.64 (d, *J* = 8.4 Hz, 2H, ArH), 6.76 (d, *J* = 8.8 Hz, 2H, ArH), 6.86 (dd, *J* = 8.8, 2.8 Hz, 1H, ArH), 7.02 (d, *J* = 8.0 Hz, 2H, ArH), 7.31 (d, *J* = 8.0 Hz, 2H, ArH), 7.70 (d, *J* = 8.8 Hz, 1H, ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 21.3, 45.6, 55.3, 55.4, 111.7, 113.0, 113.4, 121.4, 127.7, 128.5, 128.8, 129.0, 129.6, 130.4, 132.3, 136.1, 138.2, 143.2, 158.0, 159.1 ppm; MS (ESI): *m*/*z* = 422 $[M+H]^+$.