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Tetrabutylammonium chloride-triggered 6-*endo* cyclization of *o*-alkynylisocyanobenzenes: an efficient synthesis of 2-chloro-3-substituted quinolines

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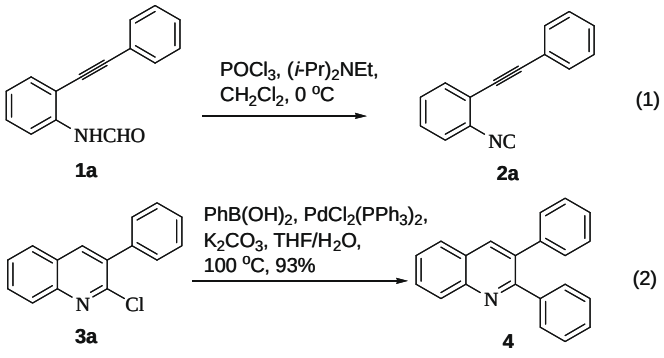
ABSTRACT

A highly efficient one-pot synthesis of 2-chloro-3-substituted quinolines has been developed by tetrabutylammonium chloride-triggered 6-*endo* cyclization of *o*-alkynylisocyanobenzenes, which are generated in situ by dehydration of the corresponding *N*-(2-ethynylphenyl)formamides.

Numerous methods for the preparation of quinoline derivatives have been developed due to their broad spectrum of biological activities such as antimalarial, antibacterial, antidiabetic, and anti-inflammatory.[1] But many of these methods suffer from the drastic reaction conditions such as high temperatures, prolonged reaction times, the need for strong bases or acids, and also unsatisfied yields. Since quinoline derivatives have become increasingly useful and important in drugs and pharmaceuticals, the development of more efficient and environmentally benign approaches is desirable.

Radicals- or nucleophiles-triggered 5-*exo* or 6-*endo* cyclization of functionalized *o*-alkynylisocyanobenzenes has recently been recognized as an efficient strategy for the synthesis of indole- or quinoline-containing heterocycles.[2] We wish to report herein a highly efficient one-pot procedure for the synthesis of 2-chloro-3-substituted quinolines by chloride-triggered 6-*endo* cyclization of *o*-alkynylisocyanobenzenes generated in situ by dehydration of the corresponding *N*-(2-ethynylphenyl)formamides. 2-Chloro-3-substituted quinolines are ideal precursors for the synthesis of diversified 2,3-disubstituted quinolines by heteroatom substitution or transition metal-catalyzed carbon–carbon bond formation at C-2.[3] 2-Chloroquinolines are usually prepared by the chlorination of 2(1*H*)-quinolones, using excess amount of phosphorus oxychloride under reflux,[3b] or from 2-vinylanilines in nitrile solvents in the presence of diphosgene,[4] or from acylanilides under the Vilsmeier conditions.[5]

During the course of synthesizing 2-(2-phenylethynyl)isocyanobenzene **2a**, we noticed that **2a** was very unstable in high concentration, although the TLC indicated that the dehydration of **1a** was complete and clean in solution (Scheme 1, Eq. 1).[6] One major by-product whose ^{1}H NMR and MS spectra matched the structure



Scheme 1. Formation of 2-(2-phenylethynyl)isocyanobenzene **2a** and Suzuki reaction of **3a**.

of 2-chloro-3-phenylquinoline **3a** was isolated. The isolated yield was about 45% based on **1a**. The structure of **3a** was further confirmed by Suzuki coupling to provide 2,3-diphenylquinoline **4** in 93% yield (Scheme 1, Eq. 2). ^{1}H NMR and ^{13}C NMR spectra of **4** were identical with the literature reports.[7]

We rationalized that the chloride was from diisopropylethylamine hydrochloride formed during dehydration of **1a** with $POCl_3$, as well as hydrolysis of excess $POCl_3$ during work-up. The isolated yield (45%) was relatively high considering the low concentration of chloride (most of the chloride should remain in aqueous phase). Therefore, the chloride-triggered 6-*endo* cyclization of **2a** should be very efficient. We speculated that in the presence of extra source of chloride, **3a** could be formed predominantly. After the formation of **2a** was complete at 0 °C for 1 h, 1.5 equiv of *n*-Bu_4NCl was added directly to the reaction mixture. The desired cyclization product **3a** was isolated in almost quantitative yield after heating at 40 °C overnight (Table 1, entry 1).

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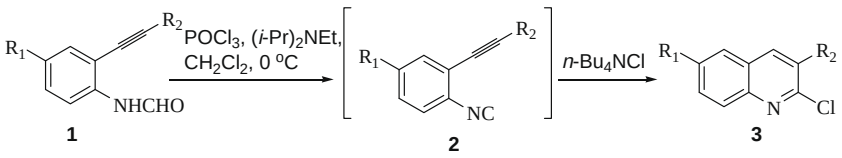
Table 1
One-pot synthesis of 2-chloro-3-substituted quinolines **3** from *N*-(2-ethynylphenyl)formamides **1**[a]



1 **2** **3**

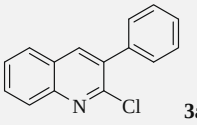
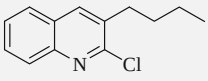
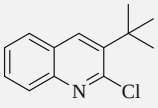
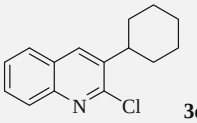
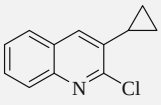
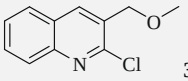
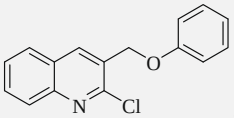
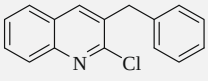
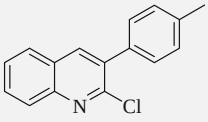
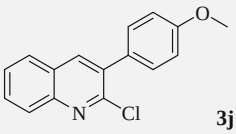
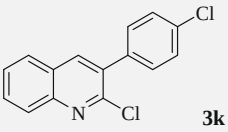
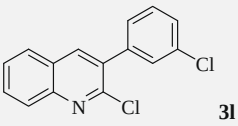
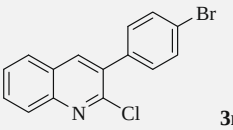
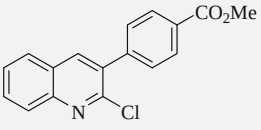
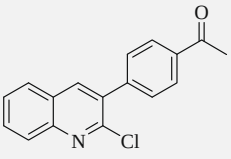
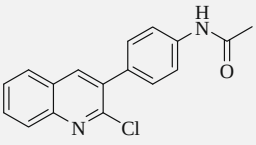
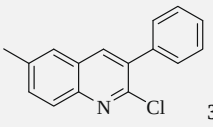
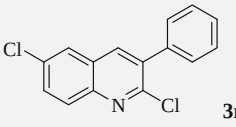
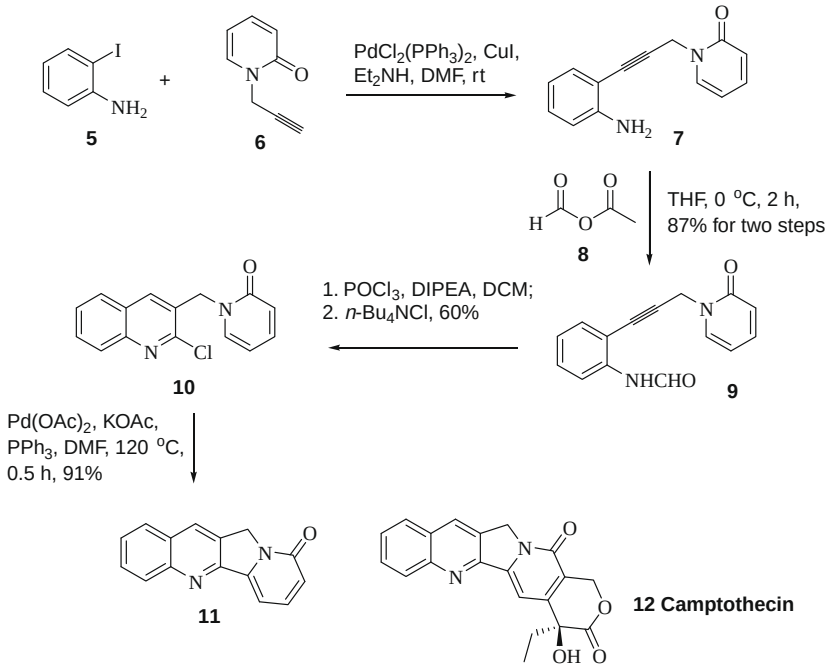
Entry	1	Temp. (°C)	Time (h)	3	Yield[b] (%)
1	**1a** R_1 = H, R_2 = Ph	40	15	 **3a**	97
2	**1b** R_1 = H, R_2 = *n*-Bu	40	15	 **3b**	97
3	**1c** R_1 = H, R_2 = *t*-Bu	60	16	 **3c**	96
4	**1d** R_1 = H, R_2 = cyclohexyl	40	12	 **3d**	93
5	**1e** R_1 = H, R_2 = cyclopropyl	40	15	 **3e**	90
6	**1f** R_1 = H, R_2 = CH_2OMe	40	15	 **3f**	89
7	**1g** R_1 = H, R_2 = CH_2OPh	40	15	 **3g**	94
8	**1h** R_1 = H, R_2 = CH_2Ph	40	15	 **3h**	91
9	**1i** R_1 = H, R_2 = 4-MeC_6H_4	40	12	 **3i**	99
10	**1j** R_1 = H, R_2 = 4-$MeOC_6H_4$	40	15	 **3j**	97

Table 1 (*continued*)

Entry	1	Temp. (°C)	Time (h)	3	Yield[b] (%)
11	**1k** R_1 = H, R_2 = 4-ClC_6H_4	40	5	 **3k**	90
12	**1l** R_1 = H, R_2 = 3-ClC_6H_4	40	3	 **3l**	98
13	**1m** R_1 = H, R_2 = 4-BrC_6H_4	40	15	 **3m**	99
14	**1n** R_1 = H, R_2 = 4-$MeO_2CC_6H_4$	40	1.5	 **3n**	95
15	**1o** R_1 = H, R_2 = 4-AcC_6H_4	40	1.5	 **3o**	93
16	**1p** R_1 = H, R_2 = 4-$AcHNC_6H_4$	40	5	 **3p**	94
17	**1q** R_1 = Me, R_2 = 4-MeC_6H_4	40	24	 **3q**	94
18	**1r** R_1 = Cl, R_2 = 4-MeC_6H_4	40	24	 **3r**	94
19	**1s** R_1 = H, R_2 = TMS	60	24		0

[a] Reaction conditions: *N*-(2-ethynylphenyl)formamides **1** (0.5 mmol), (*i*-Pr)$_2$NEt (3.0 mmol), $POCl_3$ (1.0 mmol), CH_2Cl_2 (10 mL), 0 °C for 1–2 h; *n*-Bu_4NCl (0.75 mmol), 40–60 °C, 1.5–24 h.
[b] Isolated yield.

The one-pot protocol was applied to other substrates to verify its scope and limitation (Table 1).[8] The reaction worked very well with various alkyl substituents (entries 2–8), albeit higher temperature was required for sterically hindered *tert*-butyl-substituted alkyne **1c** (entry 3). Functionalities such as cyclopropyl and ethers were tolerated (entries 5–7). The reaction worked equally well with aryl-substituted alkynes (entries 9–16). Both electron-donating and electron-withdrawing substituents delivered the products in excellent yields. Aromatic ring bearing carboxylic ester, ketone, or amide also survived (entries 14–16). Methyl and chloro substituents *para* to the isocyano group did not affect the cyclization at all (entries 17 and 18). The current two-step one-pot strategy provides a highly efficient approach to 2-chloro-3-diversified quinolines. The only exception that failed under the same reaction conditions is trimethylsilyl-substituted *o*-alkynylisocyanobenzene **2s** (entry 19). Compound **2s** is probably the most stable one among the other types of compounds. It can even be stored in its pure form which is unstable for most other *o*-alkynylisocyanobenzenes.



Scheme 2. Synthesis of the core structure of camptothecin **11**.

Steric hindrance as well as electronic effect may contribute to its stability.

Camptothecin (CPT, **12**, Scheme 2) is a naturally occurring quinoline alkaloid having remarkable antitumoral and antileukemic activity targeting DNA topoisomerase I.[9] The core structure of camptothecin family **11** can be constructed efficiently by intramolecular Heck reaction of the key intermediate 1-((2-chloroquinolin-3-yl)methyl)pyridinone **10**.[10] Compound **10** was obtained in 60% overall yield from formamide **9** by applying the current one-pot strategy. Sonogashira coupling of *o*-iodoaniline **5** with *N*-propargylated-2-pyridinone **6** afforded **7,** followed by formamide formation in high yield.

In summary, we have demonstrated a highly efficient one-pot two-step strategy for the synthesis of 2-chloro-3-substituted quinolines from in situ dehydration of *N*-(2-ethynylphenyl)formamides, followed by tetrabutylammonium chloride-triggered 6-*endo* cyclization of the resulting *o*-alkynylisocyanobenzenes. A wide range of substituents and functionalities can survive under the reaction conditions and the yields are excellent. The current strategy avoids using excess phosphorus oxychloride and multistep preparation of starting materials. The chloride on C-2 of quinolines is active enough to undergo palladium-catalyzed cross-couplings, such as intramolecular Heck reaction, to make the core structure of camptothecin.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.096.

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7. Armesto, D.; Gallego, M. G.; Horspool, W. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, *9*, 1623–1626. The spectra data of **4** agrees with the reported data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.71–7.67 (m, 1H), 7.52–7.49 (m, 1H), 7.45–7.44 (m, 2H), 7.26–7.20 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 147.4, 140.5, 140.1, 137.6, 134.6, 130.1, 129.8, 129.7, 129.5, 128.3, 128.1, 128.0, 127.5, 127.3, 127.2, 126.8.
8. *General procedure for the synthesis of* **3** *from* **1**: To a stirred solution of *N*-(2-ethynylphenyl)formamides **1** (0.5 mmol) and diisopropylethylamine (3.0 mmol) in dry DCM (10 mL), $POCl_3$ (1.0 mmol) was added dropwise within 5 min under argon atmosphere. The reaction mixture was stirred at 0 °C for 1–2 h and monitored by TLC. After the dehydration was complete, *n*-

Bu_4NCl (0.75 mmol) was added directly, and then the temperature was raised to 40–60 °C. After stirring for 1.5–24 h, the reaction mixture was poured into saturated $NaHCO_3$ (20 mL). The solution was extracted with EtOAc (20 mL × 3). The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography over silica gel with petroleum ether/EtOAc (30:1, v/v) as eluent. All products gave satisfactory spectroscopic and analytical data. *Compound* **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.54–7.44 (m, 5H); ^{13}C NMR (100 MHz, CDCl3): δ 149.6, 146.9, 138.9, 137.6, 134.8, 130.5, 129.7, 128.4, 128.34, 128.32, 127.5, 127.3, 127.2; HRMS (EI) m/z calcd for $C_{15}H_{10}ClN$ $[M+H]^+$ 240.0502, found 240.0528.

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