Synthesis of Furoquinolines by a Multicomponent Domino Process**

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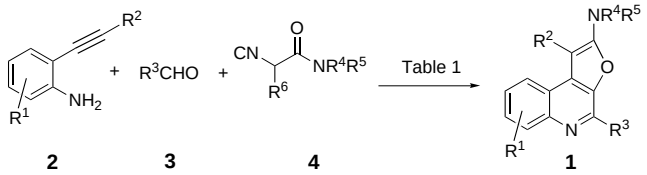
Polysubstituted furan has been found as a key structural unit in many bioactive natural products and pharmaceuticals.[1] It is also a reactive species that, upon appropriate activation, can be engaged in complex chemical transformations.[2] The development of efficient furan syntheses has thus attracted chemists for decades and continues to be an active and rewarding research area.[3,4] Besides polysubstituted furans, various annulated derivatives such as benzo-, thieno-, isoxazolo-, furo-, pyridino-, pyridazino-, and indolofuran have been synthesized and their properties investigated.[5] Cyclization of acyclic precursors and derivatization of an appropriately functionalized furan ring are two main strategies used for the elaboration of polysubstituted furans. New technologies such as solid-phase synthesis[6] and multicomponent reactions[7] have recently been developed for the preparation of this heterocycle.

Furoquinoline alkaloids, typical constituents of the *Rutaceae* and *Solanaceae* plant species, are the most widely distributed of quinoline alkaloids.[8] Antimicrobial, antitumor, and antiemetic activities have been attributed to both natural and synthetic analogues of these molecules.[9] While several synthetic routes to individual furoquinolines have been developed, most of them were linear and involved harsh reaction conditions.[10,11] In connection with our ongoing project aimed at using oxazoles as a starting point to reach diverse druglike heterocycles,[12] we report herein a conceptually novel multicomponent domino synthesis of furo[2,3-c]quinoline **1** (Scheme 1) from readily available substrates.[13,14]



Scheme 1. A three-component synthesis of furo[2,3-c]quinoline.

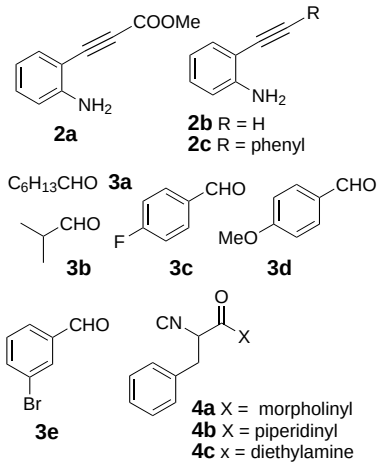
Using methyl 3-(2-aminophenyl)prop-2-ynoate (**2a**), heptanal (**3a**), and isocyanoacetamide (**4a**) as substrates, a survey of reaction conditions is summarized in Table 1. The reaction proceeded in refluxing toluene to provide the desired furoquinoline **1a** ($R^1 = H$, $R^2 = CO_2CH_3$, $R^3 = (CH_2)_5CH_3$, NR^4R^5 = morpholinyl), albeit in low yield. Both lithium bromide[15] and camphorsulfonic acid were detrimental to the desired transformation, while ammonium chloride[16] promoted the reaction sequence efficiently, providing **1a** in 75% yield.

Table 1. Three-component synthesis of furoquinoline in toluene, a survey of conditions.[a]

Entry	Additive	*t* [h]	Yield [%]
1	none	12	26
2	LiBr[b]	12	15
3	CSA[c]	12	22
4	NH_4Cl[b]	12	75

[a] Concentration of substrate: 0.1M in toluene, reaction time: 15 h, reaction temperature: RT, followed by heating under reflux. [b] 1.0 equiv. [c] 0.15 equiv. CSA = Camphorsulfonic acid.

The scope of this novel multicomponent reaction was examined using three *ortho*-alkynyl anilines,[17] five aldehydes, and three isocyanoacetamides as substrates (Scheme 2). Some



Scheme 2. Starting materials for the multicomponent reaction.

representative furoquinolines synthesized are shown in Scheme 3. The potential and general applicability of this novel three-component domino process is readily seen from these selected examples. Aniline derivatives bearing both electronically poor and electronically neutral acetylene units participated in the reaction. For the aldehyde substrate, aliphatic aldehydes, including sterically hindered isobutyraldehyde, and aromatic aldehydes bearing electron-donating or -withdrawing groups were suitable. Various substituted amino groups were easily incorporated by varying the isocyanoacetamide substrate. The presence of aryl bromide and ester functional groups in furoquinolines should, in principle, allow us to functionalize further the molecules by following standard procedures.

Various reaction pathways are possible by mixing these polyfunctionalized starting materials; the thus-observed clean reaction is remarkable. Although no detailed mechanistic study has been carried out, a reaction sequence leading to furoquinolines **1** is shown in Scheme 4. Thus, a three-component reaction between an aniline **2**, an aldehyde **3**, and an isocyanide **4** was expected to give an oxazole **7**.[12] Cycloaddition of an oxazole as an aza-diene with the properly predisposed triple bond would produce an oxa-bridged

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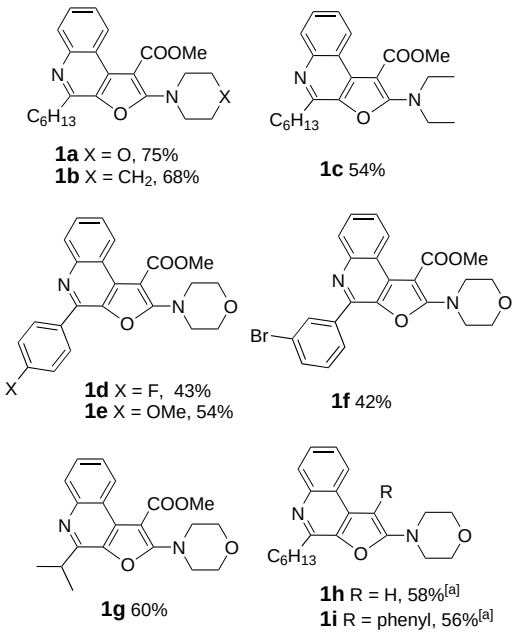
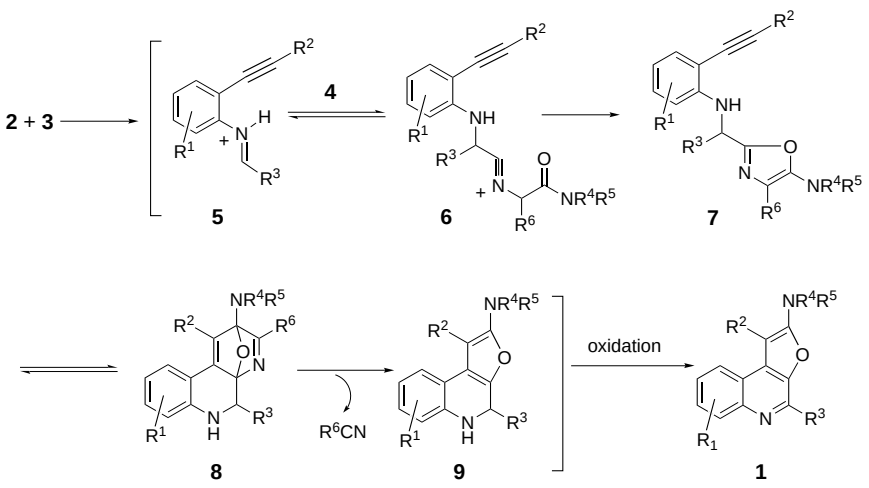


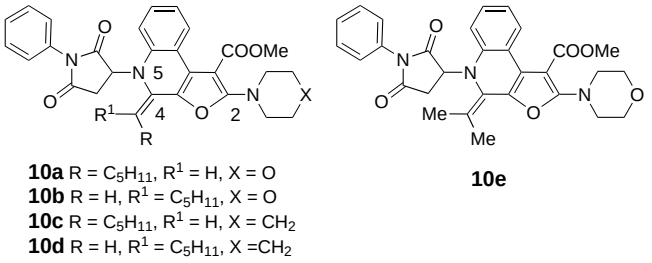
Scheme 3. Furo[2,3-c]quinolines synthesized. Conditions: NH_4Cl, 0.1 M solution in toluene, room temperature then reflux, 15 h. [a] *O*-Xylene was used as the solvent (room temperature then under reflux) for the synthesis of **1h** and **1i**.



Scheme 4. Three-component synthesis of furo[2,3-c]quinoline; a possible reaction sequence.

heterocycle **8**.[18] The latter, after extrusion of the nitrile unit by a retro-Diels–Alder reaction, would provide the furan **9**, oxidation of which by atmospheric oxygen furnished the furoquinolines **1**. At least six distinct reactions, including condensation of an aldehyde and an amine, nucleophilic addition of an isonitrile to an imine, the ring–chain tautomerization of the nitrilium intermediate, intramolecular Diels–Alder cycloaddition of oxazole, retro-Diels–Alder, and oxidation, occurred in this one-pot process. All these steps took place in an ordered manner to provide the final compound with concomitant creation of five chemical bonds. Two irreversible steps (the formation of oxazole and the retro-Diels–Alder reaction) cause the observed reaction sequence to be a unique and productive process.[19] To provide evidence for this reaction sequence, we were able to isolate and fully characterize the oxazole **7a** ($R^1 = H$, $R^2 = CO_2CH_3$, $R^3 = C_6H_{13}$, NR^4R^5 = morpholinyl, R^6 = Bn) by quenching the reaction mixture after four hours under the standard reaction conditions. Furthermore, when the anilines **2b** and **2c** were used as substrates, only the corresponding oxazoles **7** were produced even after prolonged heating in toluene. In these cases, heating a xylene solution under reflux was required to initiate and complete the cycloaddition process.

With an efficient synthesis of furo[2,3-c]quinoline in hand, its reactivity was briefly examined. Reaction of **1a** with *N*-phenylmaleiimide gave **10a** and **10b** (Scheme 5) in 73 % yield.



Scheme 5. Alder–ene products of the reaction between furo[2,3-c]quinolines and *N*-phenylmaleiimide.

Apparently, the formal Alder–ene reaction dominates over the Diels–Alder cycloaddition of furan in this polycyclic ring system, probably because of the cross-conjugation of the π systems. The presence of the 2-*N*,*N*-dialkylamino group may render the N-5 atom of the quinoline ring more nucleophilic, by analogy with the reactivity of 4-*N*,*N*-dimethylaminopyridine (DMAP). The Alder–ene adducts **10c** and **10d** were prepared in a similar manner from **1b**. Even with the furoquinoline **1g**, which bears a sterically demanding isopropyl substituent at the C-4 atom, the same type of reactivity was observed, leading to adduct **10e** in 35 % yield.

We reasoned that the conditions of this Alder–ene reaction might be compatible with the three-component synthesis of furoquinolines, hence a four-component synthesis of **10** was sought. Heating a solution of **2a**, **3a**, and **4a**, followed by addition of *N*-phenylmaleiimide, provided **10a** and **10b** in 45 % overall yield.

In conclusion, we have developed a novel, multicomponent, domino process for the synthesis of functionalized furo[2,3-c]quinoline from simple and readily accessible substrates. The significant feature of this procedure is the exploitation of the dual reactivity of both a *ortho*-alkynyl aniline (nucleophile then dienophile)[20] and an isocyanoacetamide (amphinucleophile). The operational simplicity and good chemical yield makes these novel heterocycle syntheses highly attractive in diversity-oriented parallel synthesis.[21]

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Experimental Section

A solution of the aniline **2a** (50.0 mg, 0.28 mmol), heptanal (**3a**; 46 μL, 0.34 mmol), and ammonium chloride (15.0 mg, 0.28 mmol) in toluene (3 mL) was stirred at room temperature for 1 h. The isocyanoacetamide **4a** (83.0 mg, 0.34 mmol) was added and the reaction mixture was heated under reflux for 15 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with dichloromethane. The combined organic extracts were washed with brine, dried, and the solvent removed under reduced pressure. Purification of the crude mixture by flash chromatography (SiO_2, EtOAc/heptane = 1/10 to 2/3, gradient) provided the furo[2,3-c]quinoline **1a** (83.2 mg, 75%) as an oil. IR: $\tilde{\nu}$ = 2956, 2929, 2860, 1698, 1593, 1551, 1450, 1114, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.89 (t, J = 7.4 Hz, 3H), 1.35–1.45 (m, 6H), 1.88 (q, J = 7.4 Hz, 2H), 3.13 (t, J = 7.4 Hz, 2H), 3.70 (m, 4H), 3.92 (m, 4H), 3.98 (s, 3H), 7.51 (td, J = 8.1, 1.3 Hz, 1H), 7.63 (td, J = 8.1, 1.3 Hz, 1H), 8.10 (dd, J = 8.1, 1.3 Hz, 1H), 8.92 ppm (dd, J = 8.1, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.3, 22.6, 28.6, 29.3, 31.7, 33.4, 49.4 (2C), 51.5, 66.6 (2C), 91.0, 122.3, 125.0, 126,0, 127.5, 129.4, 141.2, 145.7, 147.4, 163.6, 164.4, 167.7 ppm; MS (EI) m/z 396 [M], 397 [M+1], MS (ESI, positive mode) m/z 397 [M+1], 435 [M+K].

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