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One-pot synthesis of pyrano[4,3-*b*]quinolinones from 2-alkynyl-3-formylquinolines via oxidative 6-*endo*-*dig* ring closure

Priyabrata Roy, Binay K. Ghorai *

Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah 711 103, India

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ABSTRACT

A new regioselective one-pot procedure to synthesize pyranoquinolinones from readily available 2-alkynyl 3-formylquinolines under mild $NaClO_2/H_2O_2$ conditions in good yields has been explored. This reaction sequence, involving oxidation followed by regioselective electrophilic 6-*endo*-*dig* cyclization is more efficient over the traditional Pd(0)-mediated synthesis. When scavenger-free conditions were used, unusual chlorinated furoquinolinone derivatives were obtained.

Syntheses of various heterocycles have been a research objective for over a century, and a variety of well-established methods are available in the literature. Development of new approaches for their syntheses, employing efficient and economical routes, is currently a popular research area.[1] Substituted heterocycles are structural components of a vast number of biologically active natural and non-natural compounds. Pyranoquinolinone derivatives are of particular interest as they are known to be present in many alkaloids and possess a wide range of pharmacological and biological activities such as anticoagulant, coronary constricting, optical brightening, antifungal, antihistamine, and antiallergic effects.[2] Halogen-containing quinoline and their derivatives are of significant interest as the halogen atom plays a pivotal role in the compound's bioactivity, and such compounds provide a further avenue for structure elaboration.[3] Reported methods for the synthesis of pyranoquinolinones is limited, multistep, and suffer from poor availability of starting materials.[4]

Intramolecular cyclization through alkyne activation has emerged as an effective protocol in the preparation of a variety of heterocycles.[5] Recently, a one-pot synthesis involving oxidation followed by 5-*exo*-*dig* electrophilic cyclization of 2-alkynylbenzaldehydes for the synthesis of phthalides has been reported.[6] However, oxidative cyclization of 2-alkynyl-3-formylquinolines has not been explored so far. In this Letter, we report a one-pot highly regioselective cyclization of 2-alkynyl-3-formylquinolines **1** under environmentally friendly sodium chlorite oxidative conditions[7] that affords pyrano[4,3-*b*]quinolinones **3** through an intramolecular 6-*endo*-*dig* pathway (Scheme 1).[8]

A two-step approach to pyranoquinolinones has been examined involving: (i) preparation of 2-alkynyl 3-formylquinolines **1** and 2-alkynyl 3-formylquinoxaline **6** using the Sonogashira coupling reaction (Scheme 2)[5p] and (ii) cyclization of **1**/**6** under mild $NaClO_2$ oxidation conditions (Table 1).

Interesting observations emerge from the data in Table 1. It was observed that the aldehyde derivative **1a** was smoothly oxidized using sodium chlorite to yield the 3-substituted pyranoquinolinone **3a** in a 65% yield and no isomeric compound **3a′** was isolated (Table 1, entry 1). The reaction was performed in $MeOH/H_2O$ and since the chlorite ion is unstable at low pH, the solution was buffered with NaH_2PO_4 at pH 4.3. Hypochlorite ion (ClO_2^-) is generated in this reaction and it must be removed in order to avoid side reactions. Thirty five percent H_2O_2 was used in this regard. The effect of various organic solvents was checked with **1a** as substrate. The yield was increased using less hydrophilic alcohols (entries 1–4). No change in yield was observed when the reaction mixture was allowed to stir for a longer time (entry 5). Increase of reaction temperature (80 °C) did not improve the product yield (entry 6). Toluene greatly reduced the reaction rate, required 24 h for complete conversion of the substrate (entry 7).

Having prepared pyranoquinolinone **3a**[9] successfully, we decided to explore the scope and generality of this reaction in the synthesis of other analogues varying the substituent at C-3. Accordingly, a variety of 2-alkynyl 3-formylquinolines **1** were reacted with sodium chlorite (Table 2) under the optimized conditions (Table 1, entry 4). Various functional groups including alkyl, hydroxyl, and phenyl present in alkynes **1** were well tolerated

* Corresponding author. Tel.: +91 33 26684561; fax: +91 33 26682916.
E-mail address: bkghorai@yahoo.co.in (B.K. Ghorai).

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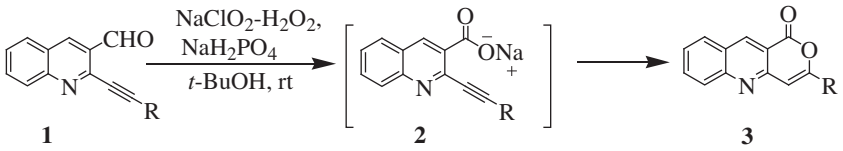
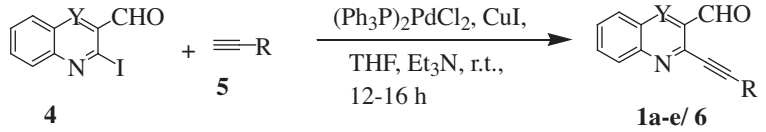
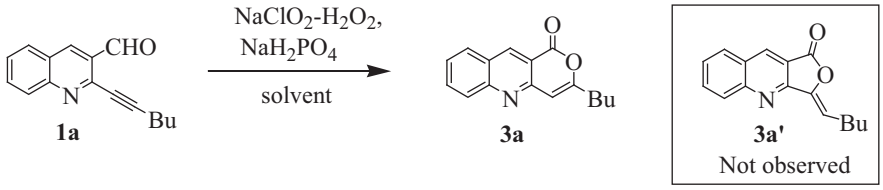


Scheme 1. Synthesis of pyrano[4,3-*b*]quinolinones.



Scheme 2. Sonogashira reaction of heteroaryl iodide with different alkynes. **1a–e**: Y=CH; quinoline series, **6**: Y=N; quinoxaline series.

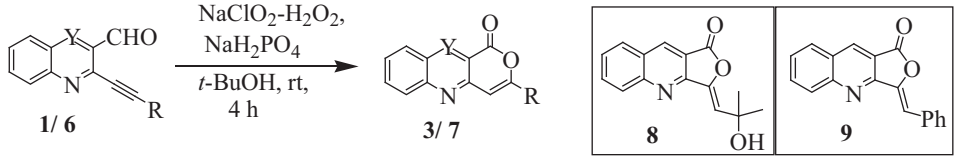
Table 1
Effect of reaction conditions on oxidative cyclization of **1a** with $NaClO_2$–H_2O_2[a]



Entry	Solvent	*T* (°C)	*t* (h)	Yield[b] (%)
1	MeOH–H_2O	25	4	65
2	EtOH–H_2O	25	4	69
3	*i*-BuOH–H_2O	25	4	71
4	*t*-BuOH–H_2O	25	4	79[c]
5	*t*-BuOH–H_2O	25	12	79
6	*t*-BuOH–H_2O	80	4	77
7	Toluene	25	24	61

[a] Reaction conditions: **1a** (1.0 equiv), $NaClO_2$ (3.7 equiv), H_2O_2 (1.2 equiv), NaH_2PO_4 (5 equiv) in a solvent at the indicated temperature and reaction time.
[b] Isolated yields.
[c] For a representative procedure see, ref. 9.

Table 2
Synthesis of pyrano[4,3-*b*]quinolinones via oxidation followed by electrophilic cyclization[a]

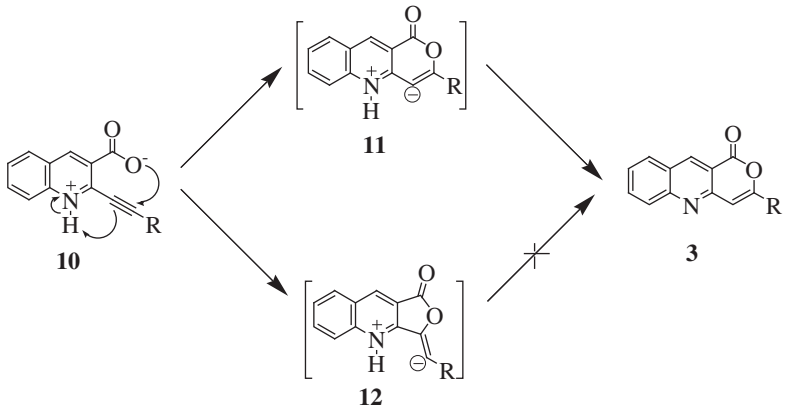


Entry	Substrate	Y	R	Product	Yield[b] (%)
1	**1a**	CH	*n*-Butyl	**3a**	79
2	**1b**	CH	$SiMe_3$	**3b**	64
3	**1c**	CH	$C(CH_3)_2OH$	**3c**	68[c]
4	**1d**	CH	Ph	**3d**	67[d]
5	**1e**	CH	CH_2OH	**3e**	73
6	**6**	N	Ph	7	70

[a] Reaction conditions: **1/6** (1.0 equiv), $NaClO_2$ (3.7 equiv), H_2O_2 (5.2 equiv), NaH_2PO_4 (5 equiv) in *t*-BuOH–H_2O (2:1/ v:v) at rt for 4 h.
[b] Isolated yield.
[c] Corresponding isomeric 5-*exo-dig* cyclized product **8** isolated in 5% yield was tentatively identified by ^1H NMR, IR, mass spectroscopy.
[d] Corresponding isomeric 5-*exo-dig* cyclized product **9** was isolated in 17% yield.

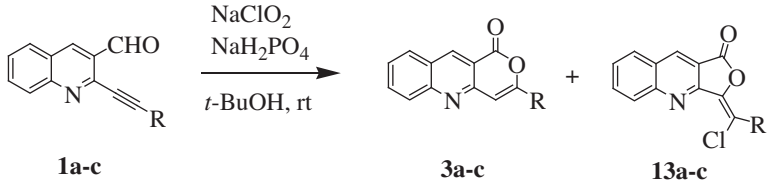
during the course of the reaction. Similar results were obtained starting from quinoxaline derivative **6** (entry 6, Table 2).

The reason for the formation of the six-membered ring over their five-member counterpart was not clear. However, a tentative mechanism, on the basis of the obtained results is proposed (Scheme 3). The cyclization process selectively proceeds via the formation of more stable anionic intermediate **11**, in which the negative charge is adjacent to electron-deficient *ortho* position of



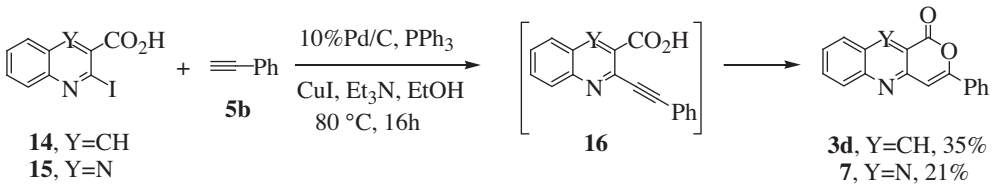
Scheme 3. Proposed mechanism for regioselectivity.

Table 3
Synthesis of pyrano[4,3-*b*]quinolinones under scavenger free $NaClO_2$ oxidation conditions[a]



Entry	Identifier **3**, **13**	R	Yield[b] **3** (%)	Yield[b] **13** (%)
1	**a**	*n*-Butyl	67	20
2	**b**	$SiMe_3$	35	55
3	**c**	$C(CH_3)_2OH$	45	35

[a] Reaction conditions: **1** (1.0 equiv), $NaClO_2$ (3.7 equiv), NaH_2PO_4 (5 equiv) in *t*-BuOH–H_2O (2:1/ v:v) at rt for 4 h.
[b] Isolated yields.



Scheme 4. Pd/C-mediated synthesis of pyranoquinolinone/quinoxalinone.

the quinoline ring. The presence of electron-donating aryl or alkyl group makes the anionic intermediate **12** unstable. Subsequently, 6-*endo-dig* cyclization is favored over 5-*exo-dig* cyclization.

During our work on converting 2-alkynyl-3-formylquinolines **1** into their corresponding pyrano[4,3-*b*]quinolinones **3** under scavenger free very mild $NaClO_2$ oxidation conditions, we observed the formation of various amounts of chlorinated 3-substituted furo[3,4-*b*]quinolinone derivatives **13** (Table 3).[7,10]

Finally, to further study the efficiency of this oxidative cyclization under mild $NaClO_2/H_2O_2$ oxidation conditions compared to the traditional Pd(0)-mediated synthesis,[11] Sonogashira-type coupling of *o*-haloheteroarylcarboxylic acid followed by electrophilic cyclization of the resulting alkyne (possessing a carboxylate in proximity to the triple bond) was briefly investigated (Scheme 4). Mechanistically, the reaction proceeds via a C–C bond forming reaction between the halide **14**/**15** and phenyl acetylene in the presence of Pd(0) generated in situ. The resulting alkyne **16** thus formed undergoes 6-*endo-dig* ring closure in an intramolecular fashion to give the desired six-membered lactone rings **3d**/**7** in poor yield compared to the conversion of **1**/**6** to **3**/**7**. The requisite halide **14**/**15** was prepared from **4** using $NaClO_2$ oxidation.

In conclusion, we have highlighted the potential of $NaClO_2/H_2O_2$ as a cheap, non-toxic system for the facile oxidative cyclization of 2-alkynyl 3-formylquinolines under mild conditions to synthesize pyranoquinolinones in good yields. Chlorinated 3-substituted furo[3,4-*b*]quinolinone derivatives were also obtained under scavenger-free conditions. Moreover, cyclization under mild $NaClO_2/H_2O_2$ oxidation conditions is a convenient, alternative method to traditional Pd(0)-mediated synthesis of pyranoquinolinone derivatives.

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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.2011.11.016.

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9. *Representative procedure.* 3-Butylpyrano[4,3-*b*]quinolin-1-one (**3a**): To a stirred mixture of 2-hex-1-ynylquinoline-3-carbaldehyde (**1a**) (237 mg, 1.0 mmol) in *t*-BuOH (10 mL) and 35% H_2O_2 (0.5 mL, 5.2 mmol) at 10 °C, a solution of $NaClO_2$ (334 mg, 3.7 mmol) and $NaH_2PO_4.2H_2O$ (780 mg, 5 mmol) in water (5 mL) was added dropwise over a period of 25 min. The resultant solution was allowed to slowly warm to room temperature with stirring over 4 h. The solution was then concentrated in vacuo to approximately half its volume. Water (20 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed on rotary evaporator and the residue was purified by column chromatography (silica gel, ethyl acetate/petroleum ether 1:4) to yield the pyranoquinolinone derivative **3a** (200 mg, 79%) as a white solid. Mp: 103–105 °C; IR (KBr, cm^{-1}): 1742 (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.09 (d, 1H, J = 8.7 Hz), 7.97 (d, 1H, J = 8.1 Hz), 7.88 (t, 1H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 6.62 (s, 1H), 2.62 (t, 2H, J = 7.5 Hz), 1.75 (pentet, 2H, J = 7.5 Hz), 1.46 (sextet, 2H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 161.8, 152.1, 150.9, 139.9, 132.9, 129.1, 128.4, 126.3 (2C), 114.7, 104.7, 33.1, 28.2, 21.7, 13.4; MS: m/e (relative intensity): 255 (MH^++1, 15), 254 (MH^+, 100); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53%. Found: C, 75.81; H, 5.87; N, 5.59.
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