The Potential of NaClO2/H2O2 as A Cheap, Non-toxic System For The Facile Oxidative Cyclization of 2-alkynyl 3-formylquinolines Under Mild Conditions to Synthesize Pyranoquinolinones

Author: Priyabrata Roy

Department of Chemistry, Victoria Institution (College), 78B, A.P.C. Road, Kolkata 700009, India

e-mail: priyo\_chem@yahoo.co.in

ABSTRACT

 NaClO2/H2O2 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 has been desribed. Chlorinated 3-substituted furo[3,4-*b*]quinolinone derivatives were also obtained under scavenger-free conditions. Moreover, cyclization under mild NaClO2/ H2O2 oxidation conditions is a convenient, alternative method to traditional Pd(0)-mediated synthesis of pyranoquinolinone derivatives.

*Keywords****:*** Pyranoquinolines, Cyclization, Heterocycles, Sonogashira coupling, Oxidation.

**1.1. INTRODUCTION**

Pyranoquinolines are an important class of compounds that constitute the basic frameworks of a number of alkaloids of biological significance, for example, geibalasine, ribalinine, flindersine, etc. (Fig. 5.1)1 and possess a wide range of pharmacological activities and biological activities such as anticoagulant, coronary constricting, optical brightening, antifungal, antihistamine, and antiallergic activities.2 Halogencontaining 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 are limited, multistep and suffer from poor availability of starting materials.4



**Figure 5.1**

The alkyne is one of the most versatile functional groups in organic chemistry.5 Significant progress has been made in intramolecular cyclization through alkyne activation.6 For example, Praveen and co-workers deloveped an effective Cu-catalyzed intramolecular hydroalkoxylation of various 2-(ethynyl)benzyl alcohols leading to the regioselective synthesis of substituted phthalans (Scheme 5.1).6b This Cu(II)-catalyzed protocol affords only the five-membered oxygenated heterocycle.



**Scheme 5.1**

The iodine-catalyzed selective synthesis of iodopyrano[4,3-*b*]quinolines from *ortho*-alkynyl aldehydes was developed by Verma and co-workers. The reaction goes through formation of cyclic iodonium intermediate (Scheme 5.2).6h,6p



**Scheme 5.2**

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 (Scheme 5.3).7



**Scheme 5.3**

1.2. **PRESENT WORK**

A series of conformationally restricted analogues (Fig. 5.2) e. g. **1** and **2** of nicotine (**3**) and anabasine (**4**) compound have been synthesized and evaluated as agonists of neuronal acetylcholine receptors (nAChRs) recently.8



**Figure 5.2**

In a continuation of our interest in the synthesis of nitrogen heterocycles,9 herein, our target was to synthesis conformationally restricted analogues **10** of nicotine (**3**) and anabasine (**4**) according to the synthetic plan depicted in Scheme 5.4. The process involves oxidation of readily available 2-iodo-3-formylquinolines **5** to the acid **6**, conversion of the acid **6** to the acid chloride, followed by amination of the acid chloride with a secondary amine to give the amide **7**. Sonogashira coupling of the amide **7** should give alkyne-amide derivative **8**, which on coupling reaction of Fischer carbene complex **9** with alkyne-amide derivative **8** should give the target molecule **10**.



**Scheme 5.4**

Having prepared the amide **7** successfully, we tried Sonogashira coupling of **7** with (trimethylsilyl)acetylene under palladium catalysis in the presence of a catalytic amount CuI. But all our efforts were failed to give the desired alkyne-amide derivative **8** in satisfactory yield. Then we have decided to carry out the Sonogashira coupling at the very first step. During the conversion of 2-alkynyl-3-formylquinolines into their corresponding acids under very mild NaClO2 oxidation conditions, we observed that the formation of various amounts of pyranoquinolinone products when the reactions were left for a certain period of time. We have decided to carry out detailed investigation of this process of conversion of alkynyl formylquinolines to pyranoquinolinones. In this chapter, a one–pot highly regioselective cyclization of 2-alkynyl-3-formylquinolines **11** under environmentally friendly sodium chlorite oxidative conditions10 that affords pyrano[4,3-*b*]quinolinones 1**3** through an intramolecular 6-*endo-dig* pathway is discussed (Scheme 5.5).11



**Scheme 5.5**

1.3. **RESULTS AND DISCUSSION**

*1.3.1.* ***Preparation of 2-alkynyl-3-formylquinoline derivatives***

The alkynyl quinaldehyde precursor necessary for our studies was obtained from acetanilide (**14**) as shown in Scheme 5.6. Conversion of **14** to 2-chloro-3-formylquinoline (**15**)12 was carried out by Vilsmeier-Haack reaction using POCl3 and DMF, and subsequent halogen exchange reaction13 of the 2-chloro-3-formylquinoline (**15**) with NaI in acetone provided 3-formyl-2-iodoquinoline (**5**). Alkynyl quinaldehyde **11** was prepared by the palladium-catalyzed Sonogashira reaction of iodoquinoline **5** with different alkyne according to the literature procedure.14,6h,6p



**Scheme 5.6**

Sonogashira coupling of 2-chloro 3-formylquinoxaline derivative **16** with phenylacetylene at room temperature under palladium catalysis in the presence of a catalytic amount CuI afforded the requisite alkynyl carbonyl derivatives **17** (Scheme 5.7).9e



**Scheme 5.7**

*1.3.2.* ***Synthesis of pyranoquinolinone derivatives***

It was observed that the aldehyde derivative **11a** were smoothly oxidized using sodium chlorite to yield the 3-substituted pyranoquinolinone **13a** in 65% yield and no isomeric compound **18** was isolated (entry 1, Table 5.1). The reaction was performed in MeOH/H2O and since the chlorite ion is unstable at low pH, the solution was buffered with NaH2PO4 at pH 4.3. Hypochlorite ion (ClO2-) is generated in this reaction and it must be removed in order to avoid side reactions. 35% H2O2 was used in this regard. The effect of various organic solvents was checked with **11a** 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).

The formation of the pyranoquinolinone **13a** was evident from spectral data. Presence of absorption band at 1742 cm-1 is due to the carbonyl group in the IR spectra. The 1H NMR spectrum of **13a** shows characteristic signals at *δ* 9.11 (s, 1H, pyridine proton), 6.62 (s, 1H)for –C*H*= and 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) for butyl group; peaks at *δ* 162.1 for –*C*O–, 104.7for –C*H*=, 33.1, 28.2, 21.7, 13.4 for butyl group along with other 9 lines in the 13C NMR spectrum and the molecular ion peak at *m/z* 254 ([M+H]+, C16H15NO2) in the mass spectrum revealed the formation of compound **13a**.

Having prepared pyranoquinolinone **13a** 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 **11** were reacted with the sodium chlorite (Table 5.2) under the optimized conditions (entry 4,

**Table 1.1** Effect of reaction conditions on oxidative cyclization of **1a** with NaClO2-H2O2*a*



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Entry Solvent T (°C) t (h) Yield (%)

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1 MeOH-H2O 25 4.0 65

2 EtOH-H2O 25 4.0 69

3 *i*-BuOH-H2O 25 4.0 71

4 *t*-BuOH-H2O 25 4.0 79

5 *t*-BuOH-H2O 25 12.0 79

6 *t*-BuOH-H2O 80 4.0 77

7 Toluene 25 24 61

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*a*Reaction conditions: **1a** (1.0 equiv), NaClO2 (3.7 equiv), H2O2 (1.2 equiv), NaH2PO4 (5 equiv) in a solvent at the indicated temperature and reaction time.

Table 5.1). Various functional groups including alkyl, hydroxyl and phenyl present in alkynes **11** were well tolerated during the course of the reaction. Similar results were obtained starting from quinoxaline derivative **17** (entry 6, Table 5.2).

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 5.8). The cyclization process selectively proceeds *via* the formation of more stable anionic intermediate **23**, in which the negative charge is adjacent to electron-deficient *ortho* position of the quinoline ring. The presence of electron-donating aryl or alkyl group makes the anionic intermediate **24** unstable. Subsequently, 6*-endo-dig* cyclization is favored over 5*-exo-dig* cyclization.

**Table 1.2** Synthesis of pyrano[4,3-*b*]quinolinones *via* oxidation followed by electrophilic cyclization*a*



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Entry Substrate Y R Product Yield (%)

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1 **11a**  CH *n*-Butyl **13a** 79

2 **11b**  CH SiMe3  **13b** 64

3 **11c**  CH C(CH3)2OH **13c** 68*b*

4 **11d**  CH Ph **13d** 67*c*

5 **11e**  CH CH2OH **13e** 73

6 **17**  N Ph **19** 70

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*a*Reaction conditions: **11/17** (1.0 equiv), NaClO2 (3.7 equiv), H2O2 (5.2 equiv), NaH2PO4 (5 equiv) in *t*-BuOH-H2O (2:1/ v:v) at rt for 4 h.

*b*Corresponding isomeric 5*-exo-dig* cyclized product **20** isolated in 5% yield.

*c*Corresponding isomeric 5*-exo-dig* cyclized product **21** was isolated in 17% yield.



**Scheme 5.8**

During our work on the conversion of 2-alkynyl-3-formylquinolines **11** into their corresponding pyrano[4,3-*b*]quinolinones **13** under scavenger free very mild NaClO2 oxidation conditions, we observed the formation of various amounts of chlorinated 3-substituted furo[3,4-*b*]quinolinone derivatives **25** (Table 5.3).7,11

**Table 1.3** Synthesis of pyrano[4,3-*b*]quinolinones under scavenger free NaClO2 oxidation conditions.*a*



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Entry Identifier **13**, **25** R Yield **13**(%) Yield **25**(%)

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1 **a**  *n*-Butyl 6720

2 **b**  SiMe3  3555

3 **c**  C(CH3)2OH 4535

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*a*Reaction conditions: **11** (1.0 equiv), NaClO2 (3.7 equiv), NaH2PO4 (5 equiv) in *t*-BuOH-H2O (2:1/ v:v) at rt for 4 h.

The pyranoquinolinones can be differentiated from the corresponding furoquinoline on the basis of several spectroscopic data, especially 1H NMR and IR spectra. On the basis of the reported comparison between the six- and five-membered lactone rings of isocoumarins (*ν*max(C=O):1710–1750 cm-1 in IR) and 3-ylidenephthalides (*ν*max(C=O): 1770–1800 cm-1 in IR) respectively. We found that our observations were in full agreement with the spectral data reported for six- and five-membered lactone rings. Moreover compound **13a**/ **13e**, singlet at *δH* (vinylic) 6.62/ 6.82, in the 1H NMR spectrum is in full agreement with their structures.15

Finally, to further study the efficiency of this oxidative cyclization under mild NaClO2/H2O2 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 5.9). Mechanistically, the reaction proceeds via a C–C bond forming reaction between the halide **26**/**27** and phenyl acetylene in the presence of Pd(0) generated *in situ*. The resulting alkyne **28** thus formed undergoes 6-*endo-dig* ring closure in an intramolecular fashion to give the desired six-membered lactone rings **13d**/**19** in poor yield compared to the conversion of **11**/**17** to **13**/**19**.



**Scheme 5.9**

1.4. **CONCLUSION**

We have highlighted the potential of NaClO2/H2O2 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 NaClO2/ H2O2 oxidation conditions is a convenient, alternative method to traditional Pd(0)-mediated synthesis of pyranoquinolinone derivatives.

**1.5 REFERENCES**

1. (a) Corral, R. A.; Orazi, O. O. *Tetrahedron Lett.* **1967**, *7*, 583; (b) Sekar, M.; Rajendra Prasad, K. J. *J. Nat. Prod.* **1998**, *61*, 294; (c) Puricelli, L.; Innocenti, G.; Delle Monache, G.; Caniato, R.; Filippini, R.; Cappelletti, E. M. *Nat. Prod. Lett.* **2002**, *16*, 95; (d) Marco, J. L.; Carreiras, M. C. *J. Med. Chem.* **2003**, *6*, 518.
2. (a) Anniyappan, M.; Muralidharan, D.; Perumal, P. T. *Tetrahedron Lett.* **2003**, *18*, 3653; (b) Ravindranath, N.; Ramesh, C.; Reddy, M. R.; Das, B. *Chem. Lett.* **2003**, *3*, 222; (c) Singer, L. H.; Kong, N. P. *J. Am. Chem. Soc.* **1960**, *88*, 5213.
3. (a) Newhouse, B. J.; Bordner, J.; Augeri, D. J.; Litts, C. S.; Kleinman, E. F. *J. Org. Chem.* **1992**, *57*, 6991; (b) Torii, E. F.; Xu, L. H.; Sadakane, M.; Okumoto, H. *Synlett.* **1992**, 513; (c) Miyachi, N.; Yanagawa, Y.; Iwasaki, H.; Ohara, Y.; Hiyama, T. *Tetrahedron Lett.* **1993**, *34*, 8267; (d) Croisey-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629.
4. (a) Jones, G. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1996; Vol. 5, pp 167; (b) Sekar, M.; Prasad, K. J. R. *J. Nat. Prod.* **1998**, *61*, 294; (c) Marco-Contelles, J.; Leόn, R.; Lόpez, M. G.; García, A. G.; Villarroya, M. *Eur. J. Med. Chem.* **2006**, *41*, 1464; (d) Butenschon, I.; Moller, K.; Hansel, W. J. *J. Med. Chem.* **2001**, *44*, 1249; (e) Kalita, K. P.; Baruah, B.; Bhuyan, P. J. *Tetrahedron Lett.* **2006**, *47*, 7779.
5. Hart, H. *In The Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; John Wiley & Sons Ltd: NY, 1994.
6. For recent examples of cycloisomerization of alkynyl substrates, see: (a) Hellal, M.; Cuny, G. D. *Tetrahedron Lett.* **2011**, *52*, 5508; (b) Praveen, C.; Iyyappan, C.; Perumal. P. T. *Tetrahedron Lett.* **2010**, *51*, 4767; (c) Jean, M.; Renault J.; Weghe, P. v. d.; Asao, N. *Tetrahedron Lett.* **2010**, *51*, 378; (d) Hellal, M.; Bourguignon, J.-J.; Bihel, F. J.-J. *Tetrahedron Lett.* **2008**, *49*, 62; (e) Layek, M.; Rao, A. V. D.; Gajare V.; Kalita, D.; Barange, D. K.; Islam, A.; Mukkanti, K.; Pal, M. *Tetrahedron Lett.* **2009**, *50*, 4878; (f) Layek, M.; Gajare, V.; Kalita, D.; Islam, A.; Mukkant, K.; Pal, M. *Tetrahedron Lett.* **2009**,*50*, 3867; (g) Gorja, D. R.; Batchu, V. R.; Ettam, A.; Pal, M. *Beilstein J. Org. Chem.* **2009**,*5*, No. 64. doi:10.3762/bjoc.5.64; (h) Verma, A. K.; Aggarwal, T.; Rustagia, V.; Larock, R. C. *Chem. Commun.*, **2010**, *46*, 4064; (i) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 62; (j) Yue, D.; Cá, N. D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581; (k) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43,* 3557; (l) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173; (m) Zhang H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43,* 1359; (n) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203; (o) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763; (p) Verma, A. K.; Rustagia, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691.
7. Lindstrom, S.; Ripa, L.; Hallberg, A. *Org. Lett.* **2000**, *2*, 2291 and references cited therein.
8. Li, J., Chin, E., Lui, A. S., Chen, L. *Tetrahedron Lett.* **2010**, *51*, 5937.
9. (a) Jana, G. P.; Ghorai, B. K. *Tetrahedron* **2007**,*63*, 12015; (b) Mukherjee, S.; Jana, G. P.; Ghorai, B. K. *J. Organomet. Chem.* **2009**, *694*,4100; (c) Jana, G. P.; Mukherjee, S.; Ghorai, B. K. *Synthesis* **2010**, 3179; (d) Roy, P.; Ghorai, B. K. *Beilstein J. Org. Chem.* **2010**,*6*,No. 52. doi:10.3762/bjoc.6.52; (e) Mukherjee, S.; Roy, P.; Ghorai, B. K. *Synthesis* **2011**, 1419.
10. For a review see: Krapcho, A. P. *Org. Prep. Proc. Int.* **2006**, *38*, 177.
11. Intramolecular cyclizations of carboxylic acids to carbon-carbon triple bonds promoted by acid goes through 6*-endo-dig* pathway, see: Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517.
12. Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc*., *Perkin Trans. 1* **1981**,1520.
13. Meth-Cohn, O.; Narine, B.; Tarnowski, B.; Hayes, R.; Keyzad, A.; Rhouati, S.; Robinson, A. *J. Chem. Soc*., *Perkin Trans. 1* **1981**,2509.
14. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**,*63*,8551.
15. Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans.* **1998**, *1*, 561.