Synthesize Pyranoquinolinones Under Mild Conditions Using NaClO2/H2O2 From 2-Alkynyl-3-formylquinolines

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ABSTRACT

Cheap and non-toxic NaClO2/H2O2 works well for the simple oxidative cyclization of 2-alkynyl 3-methanolylquinoline in mild conditions, leading to the synthesis of pyranoquinolone with good results. Chlorinated 3-substituted furo[3,4-b]quinolinone derivatives were also obtained under scavenger-free conditions. In addition, cyclization under mild NaClO2/H2O2 oxidative conditions is a suitable alternative to the conventional Pd(0)-mediated synthesis of pyranoquinolinone derivatives.

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

**1.1. INTRODUCTION**

Pyranquinolines, as for example gibarasin, ribarinin, fludexin etc. are class of compounds that form many alkaloids’ basic skeleton and have important biological properties such as (Figure 5.1).1 Also, they have many useful chemical and biological functions such as anticoagulant, optical brightening, antifungal, antihistamine and antiallergic activity.2 Halogen-containing quinolines and their derivatives have attracted interest because halogen atoms play an important role in the biological activity of these compounds and provide additional opportunities for structural design.3 The reported synthesis of pyranoquinolone is limited, multi-step, and raw materials are not easily available.4



**Figure 5.1**

Alkynes are one of the most important functional groups in organic chemistry.5 Substantial progress has been made in intramolecular cyclization of alkyne activation.6 For example, Praveen and co-workers developed the copper-catalyzed intramolecular hydroalkylation of various 2-(ethynyl)benzyl alcohols, enabling the regioselective synthesis of substituted benzofurans (Scheme 5.1).6b This Cu(II) catalytic scheme yields only five-membered oxygen-containing heterocycles.



**Scheme 5.1**

Verma and co-workers developed an iodine-catalyzed regioselective synthesis of iodopyrano[4,3-b]quinolines from 2-alkynyl aldehydes. This reaction proceeds via a cyclic iodonium intermediate formation (Scheme 5.2).6h,6p



**Scheme 5.2**

Recently, one-pot oxidation of 2-alkynylbenzaldehyde followed by *5-exo-dig* electrophilic cyclization has been reported for the synthesis of phthalides (Section 5.3).7



**Scheme 5.3**

**1.2. RECENT DEVELOPEMENT**

A series of conformationally constrained analogs of nicotine e.g.structures 1 and 2 (Figure 5.2) and anabasine (**4**) compound have been developed and evaluated as neuronal acetylcholine receptor (nAChR) agonists.8



**Figure 5.2**

Continued interest for development synthetic procedure to achieve nitrogen heterocycles,9 Pramanik and co-workers targeted to synthesis conformationally constrained 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 acid 6 to acyl chloride followed by amination of acyl 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 presence of small amount of 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 acid by mild NaClO2 oxidation conditions, they found that when the reaction was allowed to stand for a while, a pyranoquinolinone product was formed. Then they decided to carry out detailed investigation of this process of conversion of alkynyl formylquinolines to pyranoquinolinones. In this chapter, the highly regioselective one-pot cyclization of 2-alkynyl-3-formylquinoline 11 under environmentally friendly sodium chlorite oxidation condition10 to yield pyrano[4,3-b]quinolinone 13 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 their studies was obtained from acetanilide (**14**) as shown in Scheme 5.6. Conversion of **14** to chloroquinoline derivative (**15**)12 was carried out through Vilsmeier-Haack Reaction using phosphorus oxychloride 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 synthesised via Sonogashira Reaction under palladium-catalysis of iodoquinoline **5** with different alkyne according to the literature procedure.14,6h,6p



**Scheme 5.6**

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



**Scheme 5.7**

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

The aldehyde derivative (11a) was found to be successfully oxidized using sodium chlorite to give the 3-substituted pyranoquinolone (13a) in 65% yield without isolation of the isomeric compound (18) (section 1, Table 5.1). The reaction was carried out in MeOH/H2O, and since chlorite ions are unstable at low pH., the solution was buffered to pH 4.3 with NaH2PO4. Hypochlorite ions (ClO2-) are formed in this reaction and was removed to avoid side effects. 35% H2O2 was used for this. The effects of various organic solvents were studied using 11a as a substrate. Using less hydrophilic alcohol improves the yields of the product(bars 1-4). No change in results was observed when the reaction mixture was stirred for a longer time (section 5). Increasing the reaction temperature (80°C) does not increase the product yield (step 6). Toluene slows the reaction as the conversion of the substrate takes 24 hours to complete (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 2.63 (t, 2H, *J* = 7.5 Hz), 1.76 (pentet, 2H, *J* = 7.5 Hz), 1.45 (sextet, 2H, *J* = 7.5 Hz), 0.98 (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-2. 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 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).

After successfully preparing pyranoquinolinone 13a, they investigated the possibility and extent of this reaction in the synthesis of other analogues with different alkynyl group at C-2 positions. Therefore, various 2-alkynyl 3-methanoylquinolines 11 were reacted with sodium chloride (Table 5.2) under the optimum conditions (entry 4, Table 5.1). Various functional groups present in alkynes 11, including alkyl, hydroxyl and phenyl groups, are well endured during the reaction. Expected products were isolated starting from quinoxaline derivatives 17 (entry 6, Table 5.2) also.

**Table 1.1** Oxidative cyclization of **1a** with NaClO2-H2O2*a* under different reaction conditions



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Entry Solvent T (°C) t (h) Yield (%)

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1 H2O-MeOH 25 4.0 65

2 H2O-EtOH 25 4.0 69

3 H2O-*i*-BuOH 25 4.0 71

4 H2O -*t*-BuOH 25 4.0 79

5 H2O -*t*-BuOH 25 12.0 79

6 H2O -*t*-BuOH 80 4.0 77

7 Toluene 25 24 61

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*a*Reaction settings: **11a** (1.0 equiv), NaClO2 (3.6 equivalent), H2O2 (1.2 equivalent), NaH2PO4 (5 equivalent) in a solvent at the definite temperature and reaction time.

It is unclear why the six membered rings are favored over its five membered counterpart. Anyway, a tentative mechanism was proposed according to the products obtained in the reactions (Scheme 5.8). The cyclization process begins selectively by forming a stable anionic intermediate (23) that becomes negatively charged close to the electron-lacking *ortho* position of the quinoline ring. The presence of electron-rich aryl or alkyl groups destabilizes the anionic intermediate 24. Subsequently, 6*-endo-dig* cyclization outperformed 5*-exo-dig* cyclization.

**Table 1.2** Pyrano[4,3-*b*]quinolinones synthesis through oxidation followed by electrophilic cyclisation*a*



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Entree S.M. Y R Yield of Product (%)

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1 **11a**  CH *n*-butyl **13a** 78

2 **11b**  CH SiMe3  **13b** 63

3 **11c**  CH C(CH3)2OH **13c** 67*b*

4 **11d**  CH Ph **13d** 66*c*

5 **11e**  CH CH2OH **13e** 72

6 **17**  N Ph **19** 69

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*a*Reaction settings: **11/17** (1.0 equiv), NaClO2 (3.6 equivalent), H2O2 (1.2 equivalent), NaH2PO4 (5 equivalent) in *t*-butanol-H2O (1:2) at rt for 4 h.

*b*Corresponding 5-exo-dig cyclization product 20 recovered in 5% yield.

*c*Corresponding 5*-exo-dig* cyclization product **21** was recovered in 17% yield.



**Scheme 5.8**

In our study on the conversion of 2-alkynyl-3-formylquinoline 11 to the corresponding pyrano[4,3-b]quinolinone 13 under very mild NaClO2 oxidation conditions without scavengers, moderate amounts of chlorinated 3-substituted furan[3,4- b ]quinolinone derivatives 25 were observed (Table 5.3).7,11

**Table 1.3** Synthesis of pyrano[4,3-b]quinolinone by NaClO2 oxidation without scavenger.*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 settings: **11/17** (1.0 equiv), NaClO2 (3.6 equivalent), H2O2 (1.2 equivalent), NaH2PO4 (5 equivalent) in *t*-butanol-H2O (1:2) at rt for 4 h.

The pyranoquinolinones can be differentiated from the corresponding furoquinoline by the spectral data, especially 1H NMR and IR spectra. It is based on information about the six- and five-membered lactone rings of isocoumarin (νmax (C = O): 1710–1750 cm in the IR) and 3-ylidene phthalidine (νmax (C = O): 1770–1800 cm in the IR). They found that their observations were consistent with spectral data for six- and five-membered lactone rings. Moreover, compound **13a**/ **13e**, singlet at *δH* (vinylic) 6.62/ 6.82, in 1H NMR spectroscopy is in full accord with their structures.15

Finally, NaClO2/H2O2 mediated oxidative cyclisation was compared with Pd(0)-mediated Sonogashira-type coupling11 of ortho-halogen heteroaryl carboxylic acids (with carboxylic acid close to the triple bond) followed by cyclisation (Scheme 5.9). Mechanistically, the reaction occurs in the presence of Pd(0) produced in situ with halide 26/27 and phenyl alkyne. The alkyne product 28 then undergoes 6-endocyclic ring closure in an intramolecular manner to give the desired six-membered lactone ring 13d/19, which is identical to the transformation of 11/17 to 13/19, but the yield is low.



**Scheme 5.9**

1.4. **CONCLUSION**

The potential of NaClO2/H2O2 as an inexpensive, non-toxic agent for the simple oxidative cyclization of 2-alkynyl 3-formylquinolines under mild conditions to synthesize pyranoquinolinones in good yields has been highlighted in this chapter. Halogen substituted furo[3,4-b]quinolinone derivatives were also isolated 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. In addition, this cyclization under mild H2O2/ NaClO2 oxidative conditions is a suitable alternative to the conventional 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.