

THE POTENTIAL OF $\text{NaClO}_2/\text{H}_2\text{O}_2$ AS A CHEAP, NON-TOXIC SYSTEM FOR THE FACILE OXIDATIVE CYCLIZATION OF 2-ALKYNYL 3- FORMYLQUINOLINES UNDER MILD CONDITIONS TO SYNTHESIZE PYRANOQUINOLINONES

Abstract

Cheap and non-toxic $\text{NaClO}_2/\text{H}_2\text{O}_2$ works well for the simple oxidative cyclization of 2-alkynyl 3-methanolyquinoline 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 $\text{NaClO}_2/\text{H}_2\text{O}_2$ oxidative conditions is a suitable alternative to the conventional Pd(0)-mediated synthesis of pyranoquinolinone derivatives.

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

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I. 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 anti-allergic 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 pyranquinolone is limited, multi-step, and raw materials are not easily available.⁴

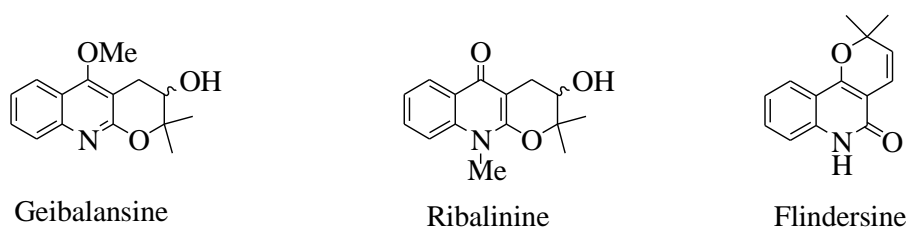
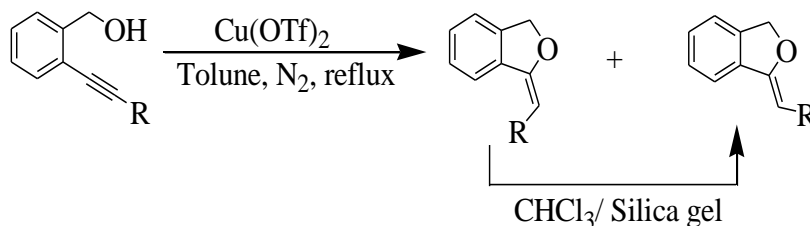


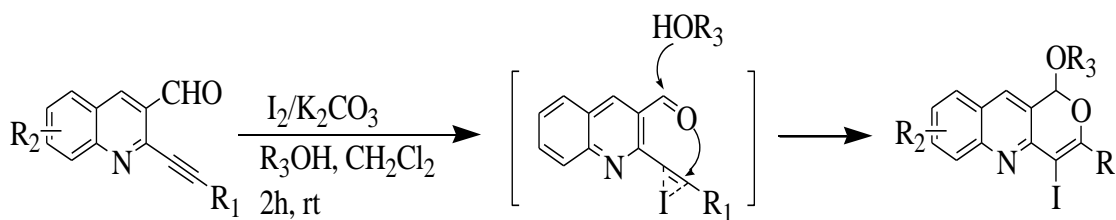
Figure 1

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.



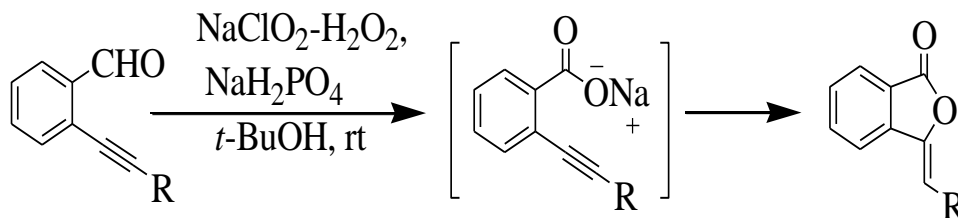
Scheme 1

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 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 3

II. RECENT DEVELOPMENT

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

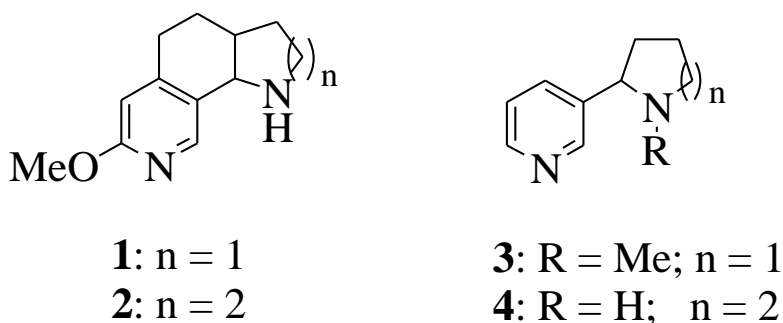
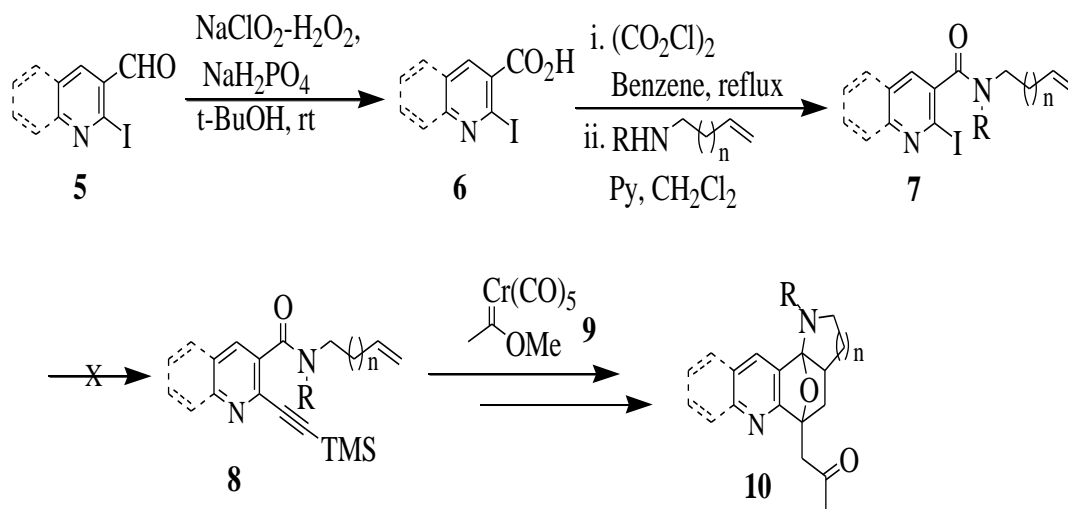


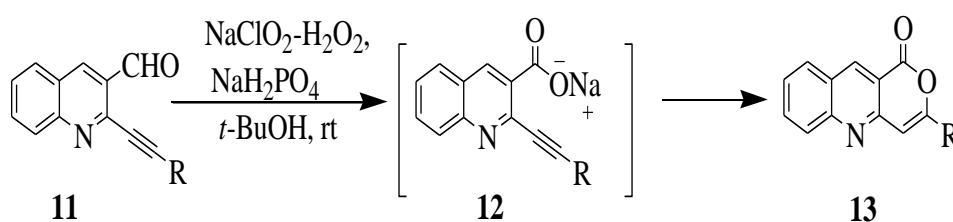
Figure 2

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 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 alkyne 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

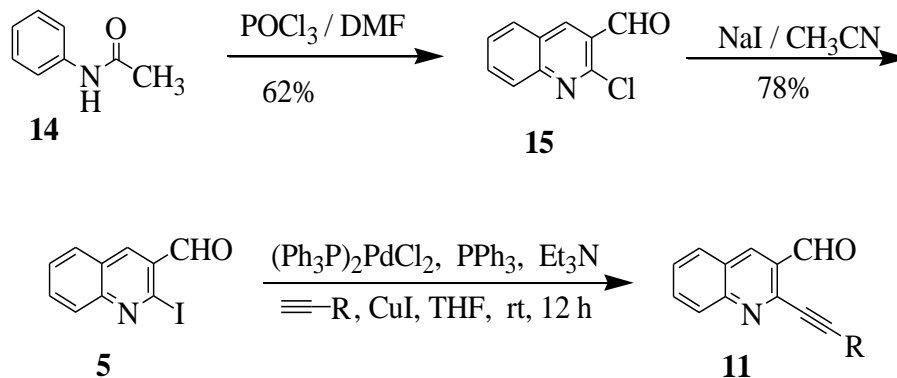


Scheme 5

III. RESULTS AND DISCUSSION

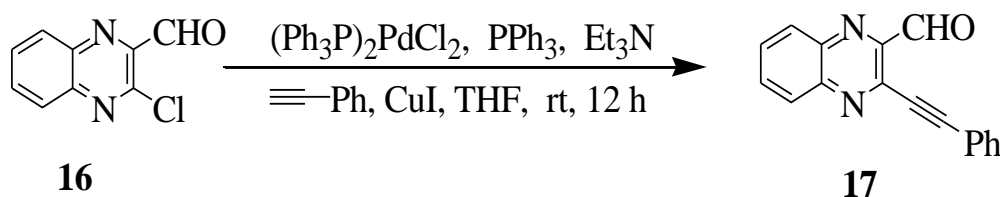
1. Preparation of 2-alkynyl-3-formylquinoline derivatives: The alkyne quininaldehyde precursor necessary for their studies was obtained from acetanilide (**14**) as shown in Scheme 5.6. Conversion of **14** to chloroquinoline derivative (**15**)¹² was carried out through Vilsmeier-Haack Reaction using 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**). Alkyne quininaldehyde **11** was

synthesised via Sonogashira Reaction under palladium-catalysis of iodoquinoline **5** with different alkyne according to the literature procedure.^{14,6h,6p}



Scheme 6

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



Scheme 7

- 2. Synthesis of pyranoquinolinone derivatives:** The aldehyde derivative (11a) was found to be successfully oxidized using sodium chlorite to give the 3-substituted pyranoquinolinone (**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 -CH= 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 -CO-, 104.7 for -CH=, 33.1, 28.2, 21.7, 13.4 for butyl group along with other 9 lines in

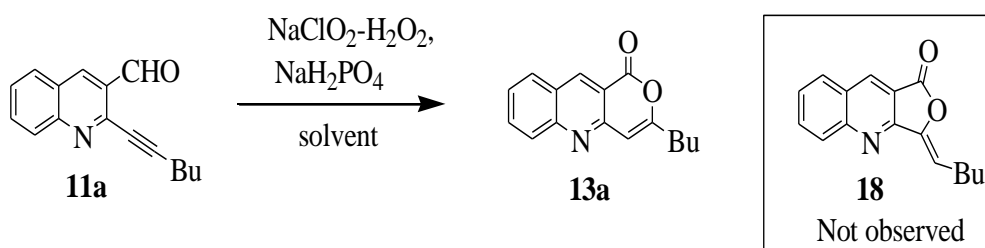
THE POTENTIAL OF NaClO₂/H₂O₂ AS A CHEAP, NON-TOXIC SYSTEM FOR THE FACILE OXIDATIVE CYCLIZATION OF 2-ALKYNYL 3-FORMYLQUINOLINES UNDER MILD CONDITIONS TO SYNTHESIZE PYRANOQUINOLINONES

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: Oxidative cyclization of 1a with NaClO₂-H₂O₂^a under different reaction conditions



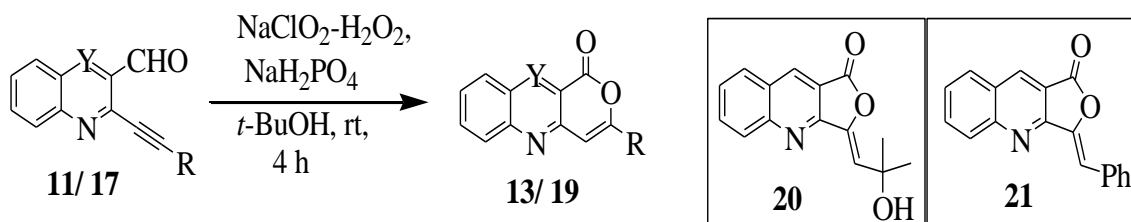
Entry	Solvent	T (°C)	t (h)	Yield (%)
1	H ₂ O-MeOH	25	4.0	65
2	H ₂ O-EtOH	25	4.0	69
3	H ₂ O- <i>i</i> -BuOH	25	4.0	71
4	H ₂ O- <i>t</i> -BuOH	25	4.0	79
5	H ₂ O- <i>t</i> -BuOH	25	12.0	79
6	H ₂ O- <i>t</i> -BuOH	80	4.0	77
7	Toluene	25	24	61

^aReaction 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 2: Pyrano[4,3-*b*]quinolinones synthesis through oxidation followed by electrophilic cyclisation^a

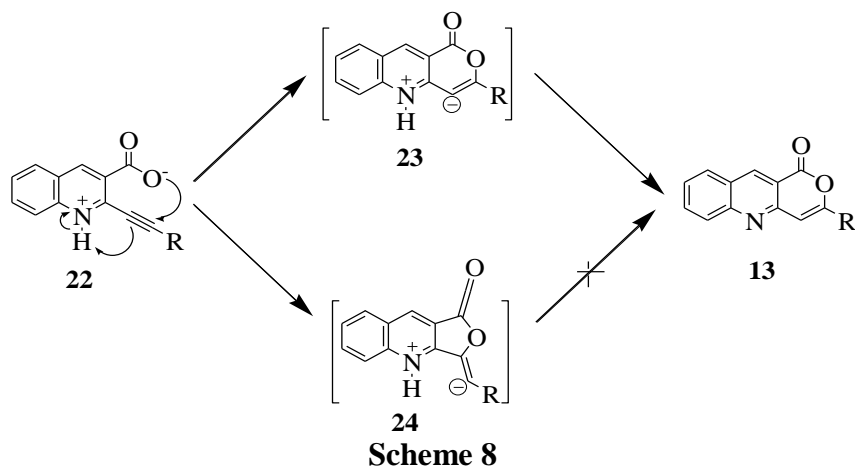


Entree	S.M.	Y	R		Yield of Product (%)
1	11a	CH	<i>n</i> -butyl	13a	78
2	11b	CH	SiMe ₃	13b	63
3	11c	CH	C(CH ₃) ₂ OH	13c	67 ^b
4	11d	CH	Ph	13d	66 ^c
5	11e	CH	CH ₂ OH	13e	72
6	17	N	Ph	19	69

^aReaction 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.

^bCorresponding 5-*exo-dig* cyclization product **20** recovered in 5% yield.

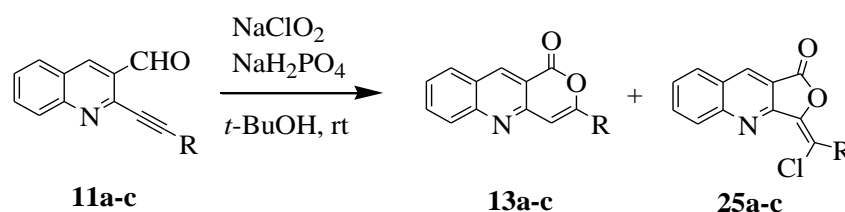
^cCorresponding 5-*exo-dig* cyclization product **21** was recovered in 17% yield.



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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 3: Synthesis of pyrano[4,3-*b*]quinolinone by NaClO₂ oxidation without scavenger.^a



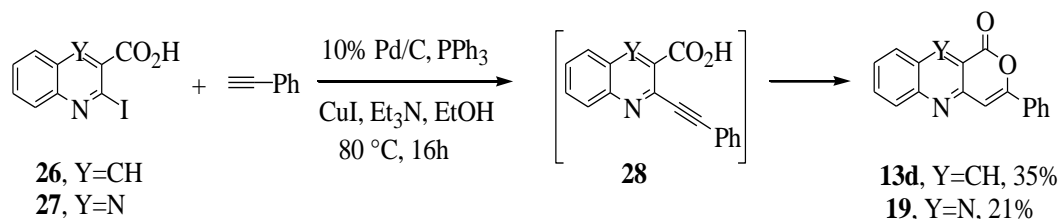
Entry	Identifier 13 , 25	R	Yield 13 (%)	Yield 25 (%)
1	a	<i>n</i> -Butyl	67	20
2	b	SiMe ₃	35	55
3	c	C(CH ₃) ₂ OH	45	35

^aReaction 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 (ν_{max} (C = O): 1710–1750 cm in the IR) and 3-ylidene phthalidine (ν_{max} (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 δ_H (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.

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Scheme 9

IV. 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.

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