Claisen Rearrangement of Hydroxynaphthoquinones: Selectivity toward Naphthofuran or α-Xiloidone Using Copper Salts and Iodine

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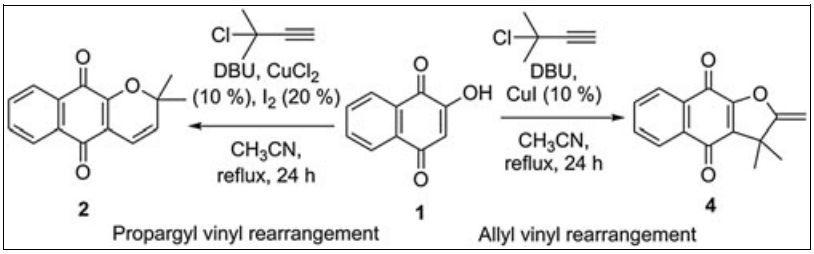

α-xiloidone is an interesting chromene that are structurally related to lapachones; in this work, we selectively synthesized α-xiloidone from the reaction of lawsone **1** with 3,3-chloro-3-methylbut-1-yne under copper/I_2 catalysis via propargyl Claisen rearrangement.

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INTRODUCTION

Since the initial publication of the Claisen rearrangement by Ludwig Claisen 100 years ago in 1912 [1], this technique remains a versatile synthetic tool, forming the basis of a large number of publications [2]. The Claisen rearrangement can be described as a [3,3]-sigmatropic transformation of allyl vinyl ethers into γ,δ-unsaturated carbonyl compounds. Some variations of this reaction include the substitution of vinyl groups, and introduction of aryl and propargyl groups, or heteroatoms (Scheme 1) [3].

The propargyl Claisen rearrangement, which is often reported as a minor branch of this topic, was first described by Black and Landor in 1965 [4], and is known to provide functionalized allenes by [3,3]-sigmatropic transformation of propargyl vinyl ethers (Scheme 1). These allenes are intermediates with further utility in the preparation of functionalized compounds and heterocycles [3]. Chromene is one of the compounds usually prepared by this methodology. The synthesis of chromenes from phenols is well-established in the literature. In particular, 2,2-dimethylchromene has specifically been described by Hlubucek in 1969 [5], Meepagalain 2010 [6], and Lykakis in 2011 [7]. 2,2-dimethyl-chromene has been produced from the reaction of phenol with 3-chloro-3-methylbut-1-yne in high yields (>95%) using diverse catalytic systems, in basic medium. Heterocyclization reactions of oxygenated rings involving structural rearrangement are less common in 2-hydroxynaphthoquinones. Recently, Perez showed that the reaction between lawsone **1** and 3,3-chloro-3-methylbut-1-yne using Cs_2CO_3, CsI (as a catalyst), and CuI in DMF furnished a furano-naphthoquinone compound in 60% yield after 24 h of reaction [8]. One of the most interesting chromenes, due to its biological activity [9–11], is α-xiloidone **2** [12]. Structurally, this compound is a naphthoquinone, related to lapachol, which is usually isolated from the bark of trees belonging to the family *Bignoneacea* [13]. α-Xiloidone has the 2,2-dimethylchromene structure, which is found in many natural derivatives. **2** can be obtained by reaction of lawsone with 3,3-chloro-3-methylbut-1-yne under thermo or metal catalysis [14], as a result of [3,3]-sigmatropic propargylic Claisen rearrangement [15]. Considering the electronic, structural, and biological features of this class of compounds [16], this study focuses on the establishment of a new and effective methodology for generating α-xiloidone **2**, from Claisen rearrangements of hydroxynaphthoquinones which is, to our knowledge, not previously described in the literature.

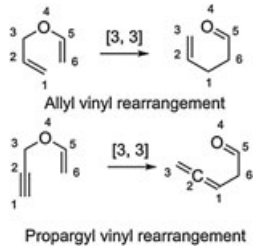
RESULTS AND DISCUSSION

Conditions adapted from the procedure described by Godfrey in 1994 were used in an attempt to prepare the propargyl ether derivative **3**, for subsequent evaluation of the cyclization to α-xiloidone **2**. To this end, 3,3-chloro-3-methylbut-1-yne was employed in the presence of DBU and $CuCl_2$ as a catalyst [14]. Interestingly, although the formation of **3** was not observed under these conditions, it was possible to isolate the desired compound **2** and the furan derivative **4** from the reaction mixture (Scheme 2).

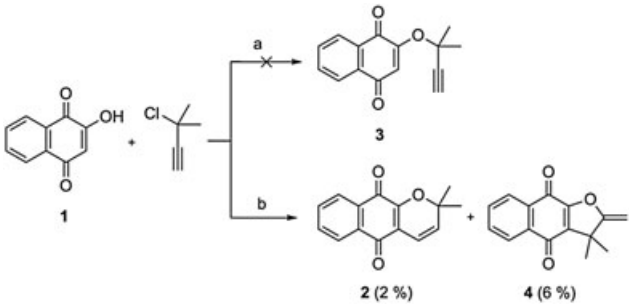
To ensure the highest yield and selectivity toward **2** or **4**, several reaction conditions were evaluated by varying the temperature, reaction time, and catalyst for optimization of the synthetic strategies, as shown in Table 1.

Based on the data obtained, it could be deduced that the selectivity for chromene or furan is dependent on type of the copper species used (i.e., Cu^+ or Cu^{+2}) and on the

Scheme 1. Allyl and propargyl vinyl Claisen rearrangement.

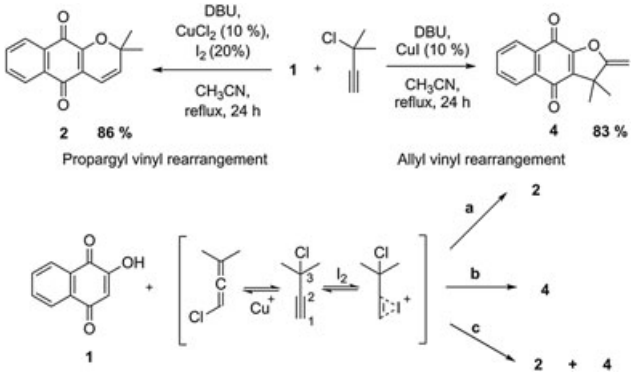


Scheme 2. Synthesis of α-xiloidone **2** and *p*-furanoquinone **4** from lawsone **1**. **a**: DBU, $CuCl_2$ (10%), CH_3CN, 0°C; **b**: DBU, $CuCl_2$ (10%), CH_3CN, reflux, 24 h.



presence of I_2 in the reaction medium. On this basis, it is possible to describe three distinct heterocyclization paths: (i) path **a**, in which the reaction selectively furnishes α-xiloidone **2**; (ii) path **b**, where the selectivity favors formation of furanonaphthoquinone **4**; and (iii) path **c**, in which a mixture of **2** and **4** is generated (Scheme 3).

Scheme 3. Summary of methodology for synthesis of α-xiloidone **2** and dunnione **4**. **Conditions**: **a**:**1**, CH_3CN, DBU, $CuCl_2$ (10 mmol %), I_2 (20 mmol %),3,3-chloro-3-methylbut-1-yne, 24 h; **b**:**1**, CH_3CN, DBU, CuI (10%),3,3-chloro-3-methylbut-1-yne, 24 h; and **c**:**1**, CH_3CN, DBU, $CuCl_2$ (10 mmol %), 3,3-chloro-3-methylbut-1-yne, 24 h.



It is proposed that the equilibrium between the alkyne-allene and alkyne-iodonium congeners that are formed *in situ* from the reactant 3,3-chloro-3-methylbut-1-yne determines the reaction path (Scheme 3). According to Grigoryan in 1982, in the presence of Cu^+, the alkyne undergoes isomerization, and the position of the chlorine atom is shifted from C-3 to C-1 [17]. Moreover, a vinyl iodide derivative may be generated in the presence of I_2 (Scheme 3) [18].

Table 1

Reaction parameters evaluated to obtain **2** and **4**, and corresponding.

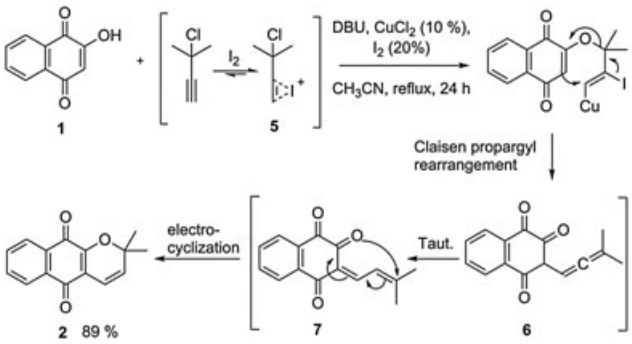
Entry	1 (mmol)	Alkyne (mmol)	Base (mmol)	Catalyst (10%)	Solvent	Procedure*	t (h)	% yield 2	% yield 4
1	1.0	2.0	DBU (1.2)	$CuCl_2$	CH_3CN	A	12	**2**	**6**
2	0.6	2.0	DBU (2.0)	$CuCl_2$	CH_3CN	A	12	**22**	**30**
3	0.6	2.0	DBU (0.7)	$CuCl_2$	CH_3CN	A	12	—	—
4	0.3	1.0	DBU (1.0)	$CuCl_2$	CH_3CN	B	12	**46**	**51**
5	0.3	1.0	DBU (1.0)	—	CH_3CN	C	3	—	**14**
6	0.1	0.5	DBU (2.0)	$CuCl_2$	CH_3CN	B	48	—	—
7	0.1	0.5	DBU (0.5)	$CuCl_2$	DMF	B	12	—	—
8	0.1	0.5	DBU (0.5)	CuI	CH_3CN	B	12	—	**83**
9	0.1	0.5	DBU (0.5)	$Cu(OAc)_2$	CH_3CN	B	12	—	—
10	0.1	0.5	K_2CO_3 (0.5)	$CuCl_2$	CH_3CN	B	24	—	—
11	0.1	0.5	DBU (0.5)	Cs_2CO_3	CH_3CN	B	24	—	—
12	0.1	0.5	DBU (0.5)	$InCl_3$	CH_3CN	B	24	—	—
13	0.6	2.0	DBU (0.5)	AgCl	CH_3CN	B	24	—	—
14	0.3	1.0	DBU (0.5)	PtO_2	CH_3CN	B	24	—	—
15	0.3	1.0	DBU (0.5)	$RuCl_3.H2O$	CH_3CN	B	24	—	—
16	0.3	1.0	DBU (0.5)	$CuCl_2$/KI (1eq)	CH_3CN	B	24	**29**	**68**
17	0.3	1.0	DBU (0.5)	$CuCl_2/I_2$ (2eq)	CH_3CN	B	24	**89**	**6**
18	0.6	2.0	DBU (0.5)	$CuCl_2/I_2$ (2eq)	CH_3CN	B	24	**86**	**4**
19	0.3	1.0	DBU (0.5)	$CuCl_2/I_2$ (4eq)	CH_3CN	B	24	**47**	**31**
20	0.3	1.0	DBU (0.5)	I_2	CH_3CN	B	24	—	—
21	0.3	1.0	DBU (0.5)	CuI/I_2 (1eq)	CH_3CN	B	24	—	—

In path **a**, **2** is obtained using $CuCl_2$ (Cu^{2+}) in the presence of I_2. In this reaction, the equilibrium is shifted to the iodonium intermediate **5**, which favors the nucleophilic attack at C-3. Subsequently, [3,3]-propargyl Claisen sigmatropic rearrangement occurs, favored by Cu^{+2}, with consequent elimination of the iodide ion, to produce the allene intermediate **6**. Then, **6** tautomerizes to the conjugated diene **7** for subsequent heterocyclization to **2** (Scheme 4).

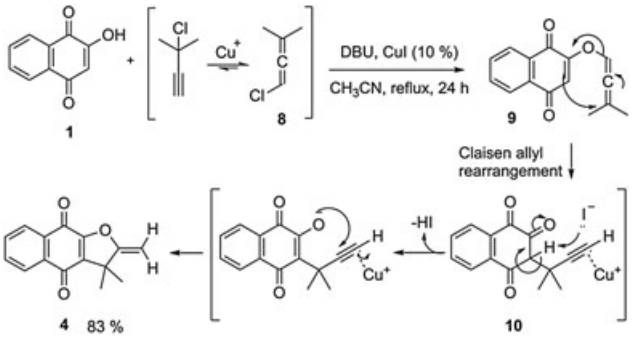
Path **b** is catalyzed by CuI (Cu^{+}) to form **4**. The cyclization for the formation of *p*-furanonaphthoquinone can be explained in terms of the displacement of the equilibrium to form the allene **8** having chlorine attached at C-1, due to the presence of Cu^{+} in the reaction medium. Thus, nucleophilic attack by the hydroxyl takes place at the C-1 position of **8** to form the allene ether **9**, with subsequent Claisen rearrangement. Unlike the process to produce **2**, in this case, there is an allyl vinyl [3,3]-sigmatropic rearrangement to yield **10**, which is a γ,δ-unsaturated carbonyl compound. Heterocyclization of **10** leads to formation of **4**, possibly favored by the complexation of intermediate **10** with Cu^{+} (Scheme 5) as previously described [8].

Finally, path **c** involves the formation of products **2** and **4**, demonstrating the equilibrium between the two isomeric forms of the alkyne, which compete for the following allyl or propargyl rearrangements (Scheme 6).

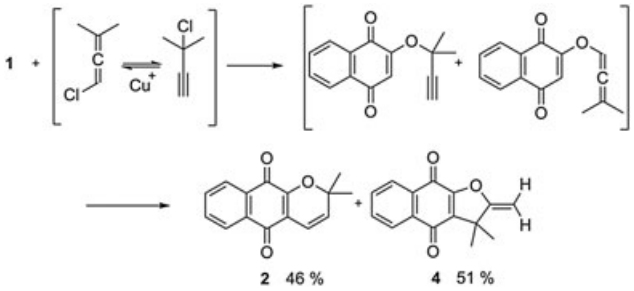
Scheme 4. Proposed mechanism for selective formation of **2**.



Scheme 5. Proposed mechanism for selective formation of **4**.



Scheme 6. Proposed mechanism for path **c**.



The formation of a furan or pyran ring from **1** can be modulated by variation of the catalytic system (source of copper and iodine). The propargyl Claisen rearrangement dominates when Cu^{2+}/I_2 is used, with consequent formation of **2**. In contrast, Claisen rearrangement of the allyl vinyl type is favored in the presence of Cu^{+} catalysts under similar conditions (Table 1, entry 21). In addition, other parameters, such as the amount of base, temperature, and time are directly correlated to the reaction yields.

CONCLUSIONS

This paper presents a new route for the synthesis of α-xiloidone **2** based on propargyl Claisen [3,3]-sigmatropic rearrangement and synthesis of the furan **4**, which can be used as α-dunnione precursor [8], via allyl vinyl Claisen [3,3]-sigmatropic rearrangement. This procedure offers the economic advantage of lower cost of the catalysts relative to the catalysts employed in prior syntheses of **2**. Thus, this technique is a promising method for achieving selective formation of chromenes and furanic derivatives of naphthoquinones from lawsone **1**, such as **2** and **4**, respectively. Other advantages of the proposed method, in addition to the lowered cost and simplicity of the catalytic reagent, include improved yields, and fewer reaction steps, providing more material for studies involving this class of compounds that are underexplored from the medicinal chemistry perspective, in addition to further expanding the database on Claisen rearrangements 100 years after it was first published.

EXPERIMENTAL

2,2-dimethyl-2H-benzo[g]chromene-5,10-dione (2). To a solution of **1** (0.56 mmol, 100 mg) in CH_3CN (20 mL) under stirring at 0°C, was added DBU (2 mmol, 0.28 mL), Copper (II) chloride (57 μmol, 7.6 mg), I_2 (28.5 μmol, 14.4 mg) and 3,3-chloro-3-methylbut-1-yne (2 mmol, 0.22 mL). The reaction was heated until room temperature and then refluxed for 24 h. The solvent was removed under reduced pressure and the residue was poured into cold water, the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine solution and dried by Na_2SO_4. The solvent was removed under reduced pressure and purified by flash column

chromatography (hexane/ethyl acetate, 9:1) to afford a orange crystal, **2**, 89%. mp: 156°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.49 (s, 6H), 5.64 (d, $J = 12$ Hz, 1H), 6.57 (d, $J = 9$ Hz, 1H), 7.63 (m, 2H), and 8.01 (m, 2H). ^{13}C-RMN (75 MHz, $CDCl_3$): δ 181.9, 179.8, 152.4, 133.9, 133.2, 131.6, 131.5, 130.8, 126.2, 117.9, 117.8, 115.5, 80.5, and 28.4. IR (cm^{-1}): 2918, 2357, 1651, 1271, 966, and 717. HRMS: (M^{+1}) calculated to $C_{15}H_{13}O_3^+$: 241.0859, obtained: 241.0856

3,3-dimethyl-2-methylene-2,3-dihydronaphtho[2,3-b]furan-4,9-dione (4). To a solution of **1** (0,14 mmol, 25 mg) in CH_3CN (10 mL) under stirring at 0°C, was added DBU (0.5 mmol, 0.07 mL), CuI (14 µmol, 2.6 mg) and 3,3-chloro-3-methylbut-1-yne (0.5 mmol, 0.055 mL). The reaction was heated until room temperature and then maintained under reflux for 24 h. The solvent was removed under reduced pressure and the residue was poured into cold water, the aqueous phase was washed with ethyl acetate (3×10 mL). The organic layer was washed with brine solution and dried by Na_2SO_4. The solvent was removed under reduced pressure and purified by flash column chromatography (hexane/ethyl acetate, 9:1) to afford a yellow crystal, 83%. mp 137°C. ^{1}H-RMN (300 MHz, $CDCl_3$): δ 1.52 (s, 6H), 4.4 (d, $J = 3$ Hz, 1H), 4.86 (d, $J = 6$ Hz, 1H), 7.66 (m, 2H), and 8.02 (m, 2H). ^{13}C-RMN (75 MHz, $CDCl_3$): δ 181.24, 177.08, 169.9, 156.0, 134.33, 133.19, 133.14, 131.5, 131.2, 126.34, 126.2, 87.14, 45.43, and 28.13. IR (cm^{-1}): 2918, 2357, 1651, 1271, 966, and 717. HRMS: (M^{+1}) calculated to $C_{15}H_{13}O_3^+$: 241.0859, obtained: 241.0855

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