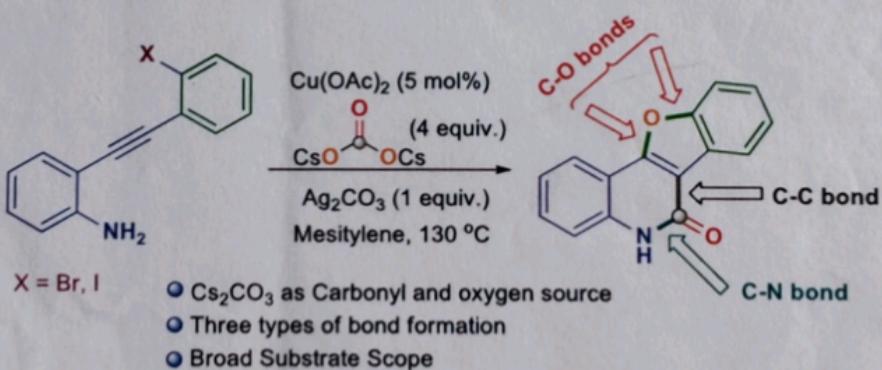


Cs₂CO₃ as Source of carbonyl and Ethereal Oxygen in Cu-Catalyzed Cascade Synthesis of Benzofuro[3,2-*c*]quinolin-6(5*H*)-ones

Abstract: Simultaneous construction of C–C, C–O, and C–N bonds utilizing Cs₂CO₃ as the source of both carbonyl (CO) and ethereal oxygen; a cascade synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-one has been achieved using Cu(OAc)₂ and Ag₂CO₃ combination. Preliminary studies of the reaction mechanism reveal that both carbonyl and ethereal oxygen in the product originates from Cs₂CO₃. The synthetic utility of the approach are demonstrated by versatile chemical transformations. A plausible reaction mechanism has been proposed for this unprecedented transformation.



Introduction

In modern era of organic chemistry, synthesis of highly functionalized and structurally complex heterocycles is a challenging task. Cascade reactions, in this regard is one of the most promising approaches that can resolve the aforesaid challenge.¹ Formation of several C–C and C–heteroatom bonds for rapid access to fused and complex polycyclic skeleton in a single operation with a sequence of reactions occurring in tandem is the attractive feature of a cascade reaction. Recently this kind of strategy has proven a powerful “Synthetic Avenue” for the conversion of internal alkynes into biologically interesting polycyclic² or spiro heterocycles.³ Alkynes that are tethered to substrates containing nucleophilic functional groups at appropriate positions are often utilized as substrates for metal-catalyzed cascade transformations.⁴ The substrate may be prefunctionalized with the nucleophile or alternatively introduced into the substrate via a Ullman type cross-coupling reaction. Copper as catalyst has great potential in initiating both Ullman coupling as well as cascade reactions⁵. Hence, copper catalyzed domino synthesis of cyclic compounds via a combination of Ullman coupling with subsequent cascade cyclization is receiving much attention these days.⁶. In continuation to our efforts towards the copper catalyzed synthesis of heterocyclic system⁷ we assume that the reaction of 2-((2-bromophenyl)ethynyl)aniline with α -amino acid under copper catalysis would lead to the formation of fused heterocyclic system via amination followed by aerobic oxidative cyclization and decarboxylation. To evaluate the envisioned proposal a model reaction was carried out between 2-((2-bromophenyl)ethynyl)aniline (0.2 mmol) and L-alanine (2 equiv.) in the presence of Cu(OAc)₂ (10 mol%) as catalyst and Cs₂CO₃ (3 equiv.) as base in mesitylene at 130 °C. Spectroscopic analysis (NMR, IR and HRMS analysis) and crystal structure of one of the derivatives confirm its structure as quinolin-2(1H)-one fused with benzofuran i.e. benzofuro[3,2-*c*]quinolin-6(5*H*)-one. The product structure brings about two interesting ends of this transformation; the incorporation of carbonyl as well as oxygen in the resultant heterocycle and the sources of them.

To find the source of carbonyl group in the newly formed product a control reaction was carried out. The two possible sources of carbonyl in this reaction could be either the reagents L-alanine or Cs₂CO₃. A reaction carried out under otherwise identical condition in the absence of amino acid L-alanine, gave the same product without any alteration in the yield. This confirms that Cs₂CO₃ is the only source of carbonyl in the newly formed product. To know, whether other inorganic carbonates or bicarbonates would behave similar to Cs₂CO₃, the same reaction was performed with a number of inorganic bases such as K₂CO₃, Na₂CO₃, KHCO₃, as well as

NaHCO_3 . Except K_2CO_3 which furnished product in < 8%, all other reactions failed completely. This result establishes that Cs_2CO_3 is the best of the lot that selectively serves as carbonyl source.

Benzofuro[3,2-*c*]quinolin-6(5*H*)-one derivatives shows interesting activity for osteoporosis and potential antimalarial agent.⁸ Some derivatives of benzofuro[3,2-*c*]quinolin-6(5*H*)-one showing pharmaceutical activity are shown in Figure 1. Surprisingly, the literature contains only a few reports describing the synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-ones.^{8,9}

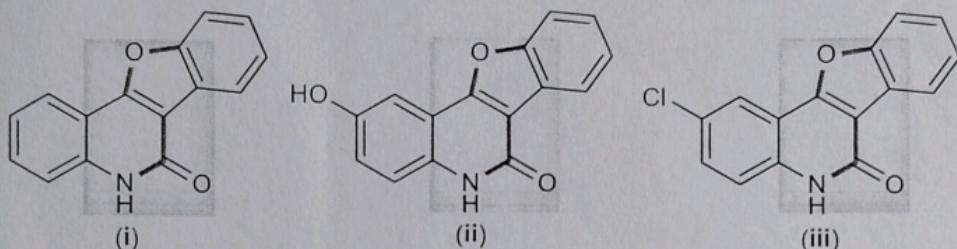
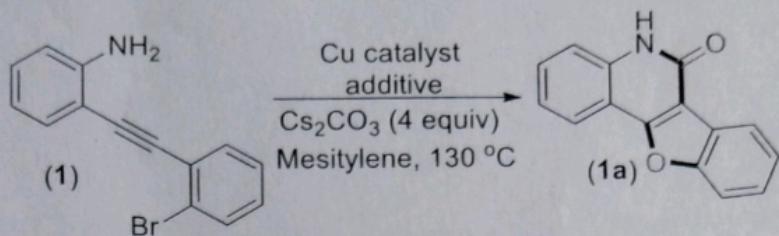


Figure 1. Molecules showing antimalarial activity.

It is well established that metal carbonates and bicarbonates act as CO_2 source. However, until now Cs_2CO_3 has been reported to serve as CO_2 source for the synthesis of cyclic or acyclic carbonates.¹⁰ Recently, Gao *et al.* reported Cs_2CO_3 as oxygen source for the synthesis of ester by the coupling of acid chloride and alkyl halide.¹¹ So far synthesis of biologically active heterocycles by using CO_2 generated from metal carbonates is unfamiliar. On the other hand, gaseous CO_2 have been extensively utilized for the synthesis of carbonates, acid, ester and lactone etc.¹² Silver catalyzed incorporation of gaseous CO_2 in a variety of internal and terminal alkynes, allenes, *o*-alkynylacetophenone, and allylsilane as well as carboxylation of terminal alkynes are summarized by Yamada *et al.*¹³ in his recent review. This inserted CO_2 undergo various kind of rearrangement to afford the different heterocycles.¹³ Similarly, copper catalyzed incorporation of CO_2 in to alkene, alkyne, allene and other system have been reported by various other groups.¹⁴ To the best of our knowledge, the reaction process where CO_2 from Cs_2CO_3 is utilized for the cascade synthesis of benzofuro[3,2-*c*]quinolin-6(5*H*)-ones reported for the first time.

Table 1. Screening of reaction conditions.

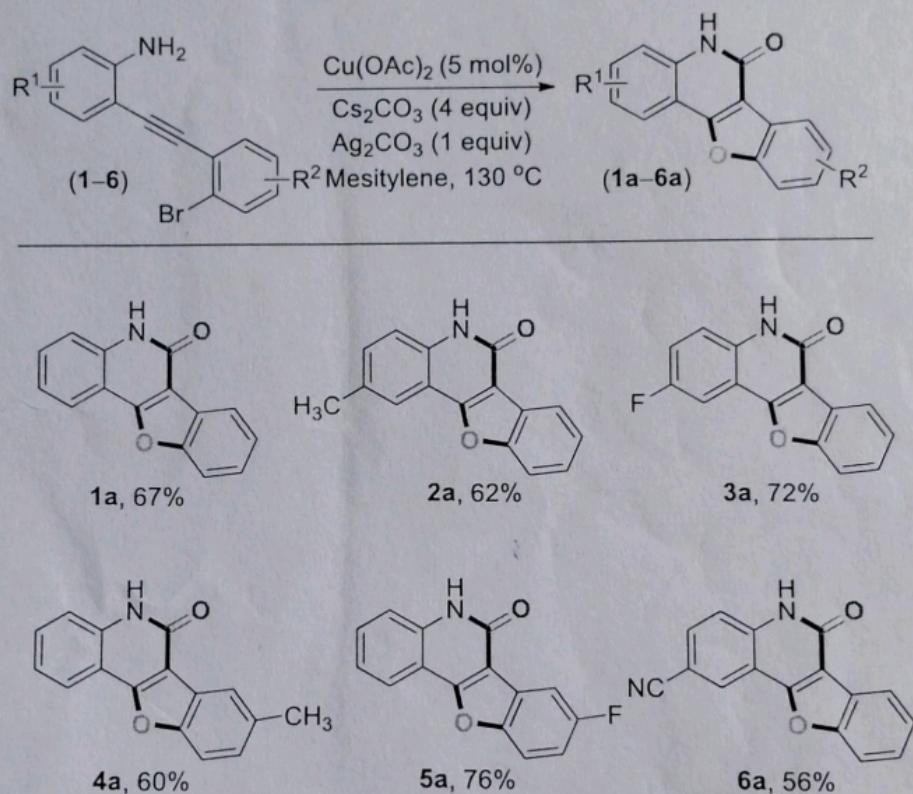
Entry	Catalyst (mol %)	Cs ₂ CO ₃ (equiv)	Additive (equiv)	Yield ^a
1	Cu(OAc) ₂ (10)	Cs ₂ CO ₃ (4)	-	62
2	Cu(OTf) ₂ (10)	Cs ₂ CO ₃ (4)	-	59
3	Cu(C ₅ HF ₆ O ₂) ₂ (10)	Cs ₂ CO ₃ (4)	-	53
4	CuBr ₂ (10)	Cs ₂ CO ₃ (4)	-	52
5	CuCl ₂ (10)	Cs ₂ CO ₃ (4)	-	56
6	CuI (10)	Cs ₂ CO ₃ (4)	-	60
8	CuBr (10)	Cs ₂ CO ₃ (4)	-	56
9	CuCl (10)	Cs ₂ CO ₃ (4)	-	51
10	Cu(OAc) ₂ (10)	Cs ₂ CO ₃ (4)	Ag ₂ CO ₃ (1)	69
11	Cu(OAc) ₂ (10)	-	Ag ₂ CO ₃ (4)	00
12	Cu(OAc) ₂ (10)	Cs ₂ CO ₃ (4)	Ag(OCOCF ₃) (1)	61
13	Cu(OAc) ₂ (10)	Cs ₂ CO ₃ (4)	Ag(OSO ₂ CF ₃) (1)	54
14	Cu(OAc) ₂ (20)	Cs ₂ CO ₃ (4)	Ag ₂ CO ₃ (1)	69
15	Cu(OAc)₂ (5)	Cs₂CO₃ (4)	Ag₂CO₃ (1)	67

^a isolated yield

Overwhelmed by this unprecedented result, we further optimized the reaction parameter to enhance the efficiency with 2-((2-bromophenyl)ethynyl)aniline as model substrate. First, different copper salts [Cu(OAc)₂, Cu(OTf)₂, Cu(C₅HF₆O₂)₂, CuBr₂, CuCl₂, CuI, CuBr, CuCl] were scrutinized (Table 1, entries 1–9). All the copper salts tested gave the product (**1a**) in a comparable yield as can be seen from Table 1. However, Cu(OAc)₂ proved to be optimal for the formation of (**1a**) (Table 1 entry 1). The use of Ag₂CO₃ as an additive enhanced the yield of cyclized product by 6% (Table 1, entry 10). The increment in the product yield with use of Ag₂CO₃ leaves a question, whether it also act as carbonyl source similar to Cs₂CO₃. To find the answer, a reaction was performed under otherwise identical conditions in the absence of Cs₂CO₃ using 4 equivalents Ag₂CO₃ (Table 1, entry 11). Complete failure of product formation reconfirms that Cs₂CO₃ is solely responsible for the newly introduced carbonyl functionality and

Ag_2CO_3 might be helping during the cyclization process. With $\text{Cu}(\text{OAc})_2$ as catalyst and Cs_2CO_3 as carbonyl source other silver salts like $\text{Ag}(\text{OCOCF}_3)$ and $\text{Ag}(\text{OSO}_2\text{CF}_3)$ were also examined (Table 1, entry 13 and 14); however Ag_2CO_3 turned out to be most effective (Table 1, entry 10). While an increased catalyst loading was not beneficial (Table 1, entry 14), but it can be lowered to 5 mol % (Table 1, entry 15) without any alteration in the product yield. Finally, the optimized conditions for this transformation include use of $\text{Cu}(\text{OAc})_2$ (5 mol%), Cs_2CO_3 (4 equiv.), Ag_2CO_3 (1 equiv.) in mesitylene (3 mL) at 130 °C.

Scheme 1. Substrate scope of cascade cyclization.^{a,b}



^aReaction conditions: **1–6** (0.2 mmol), $\text{Cu}(\text{OAc})_2$ (5 mol%), Cs_2CO_3 (0.8 mmol, 4 equiv), Ag_2CO_3 (0.2 mmol, 1 equiv), mesitylene (3 mL) at 130 °C for 24 h. ^bIsolated pure product.

With the above optimized condition in hand, we set out to explore the generality and scope of this protocol and the experimental results are summarized in Scheme 1. Initially, the effect of substituents on the amine bearing ring was explored. The presence of electron-donating groups such as *p*-Me (**2**) on the aromatic ring gave their corresponding products (**2a**) in 62% yields. The yields so obtained were lower than the unsubstituted analogue (**1a**). Presence of moderately electron-withdrawing groups such as *p*-F (**3**) gave identical yields of their products (**3a**, 72%) unsubstituted analogue (**1a**). The structure of the product (**3a**) has been unequivocally established

by single crystal X-ray crystallography (Figure 2). Similar trend in electronic effect was observed for both electron-donating and electron-withdrawing substituents when present in the other ring. The presence of electron-donating groups such as *p*-Me (**4**) in the halogen bearing aromatic ring gave products (**4a**) in 60% yields. Further, moderately electron-withdrawing groups such as *p*-F (**5**) in the halogen bearing aromatic ring gave marginally better yields of the product (**5a**, 76%) to that of amine bearing ring (**3a**). The presence of strongly electron-withdrawing group *p*-CN (**6**) provided inferior yield (56%) of product (**6a**). In any cascade reaction several bond making and bond breaking process takes place from multiple directions bearing substituents at various sites. Thus, it is difficult to correlate the true electronic factor and ascertain the exact rate determining step in the reaction on the basis of final yields. When the bromo substituent was replaced with an iodo group the yields of their products were marginally better than their bromo analogues as demonstrated during the synthesis of (**1a**) (Scheme 1).

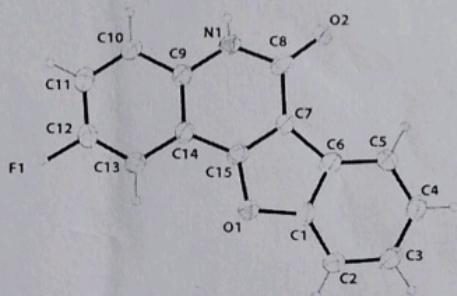
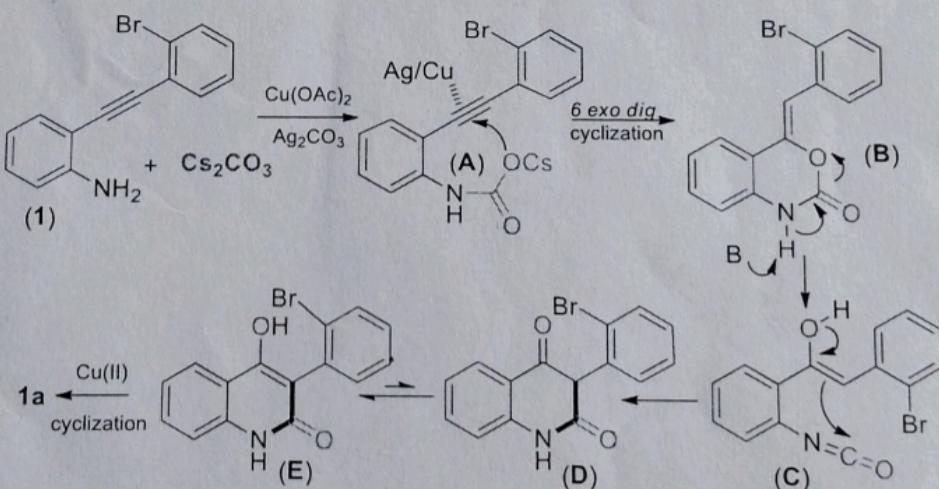


Figure 2. Ortep View of **3a**.

To understand the nature of this unprecedented carbonylation-etherification process and to gain insight into the reaction mechanism, further investigations were carried out. The source of carbonyl in the quinolone part has already been accounted for; however the source of ethereal oxygen in the benzofuran ring is yet to be ascertained. The possible source of ethereal oxygen could be either the aerial oxygen or the traces of water present in the commercial grade mesitylene. Comparable yield of (**1a**) was obtained when the reaction was performed under an argon atmosphere, suggesting aerial oxygen not to be the source of benzofuran oxygen. Another reaction performed using anhydrous mesitylene under an inert atmosphere in an otherwise identical conditions, gave the desired product (**1a**) in 59% yield. This result ruled out moisture/H₂O in commercial grade mesitylene not to be the source of ethereal oxygen in (**1a**). This leaves Cs₂CO₃ as the only possible source of oxygen in benzofuran moiety.¹¹ There are reports where aryl halides undergo hydroxylation in the presence of base and copper catalyst.¹⁵ During this cascade cyclization, the *ortho* bromo group is replaced with an oxygen atom therefore, initial *ortho* hydroxylation via copper catalysis with an appropriate oxygen source

(possibly Cs_2CO_3) cannot be completely ruled out. To check the possibility of hydroxylation path when a presynthesized 2-((2-aminophenyl)ethynyl)phenol (**1'**) was subjected to the present reaction condition failed to give the expected product (**1a**) even after 36 h. This ruled out any possibility of initial hydroxylation via Ullmann coupling path. During the synthesis of 4-hydroxyquinolin-2(*H*)-ones the carbonyl and oxygen both originated from CO_2 via the intermediacy of isocyanate as demonstrated by Yamada *et al.*^{13g} Thus, a reaction was carried out in an atmosphere of CO_2 using DBU as the base but in the absence of Cs_2CO_3 under similar reaction conditions. Formation of product (**1a**) in 42% yield suggests that both ethereal oxygen and the carbonyl groups originate from CO_2 (i.e. Cs_2CO_3).

Based on the above experimental results, a probable reaction pathway is illustrated in Scheme 2. The process starts with the initial *N*-carboxylation with Cs_2CO_3 to give species **A**, which undergo *6-exo-dig* cyclization that is assisted by Cu/Ag salts giving a cyclic carbamate intermediate **B**. A base mediated ring opening of intermediate **B** gave intermediate isocyanate **C**. Intermediate **C** undergo intramolecular cyclization (C–C bond formation) to generate a 1,3-diketone intermediate **D**. Enolization of **D** to **E** followed by an intramolecular Ullmann coupling (C–O bond formation) produces benzofuro[3,2-*c*]quinolin-6(*H*)-one (**1a**) (Scheme 2). Formations of intermediates **B**, **C**, **D** and **E** in the reaction have been detected by HRMS analysis of the reaction mixture at various time intervals.



Scheme 2. Plausible mechanism for Cs_2CO_3 acting as both carbonyl and oxygen source.

In conclusion, we have developed a novel protocol for the synthesis of benzofuro[3,2-*c*]quinolin-6(*H*)-one derivatives catalyzed by copper. Concomitant installation of three types of bonds *viz.* two C–O and one each of C–C and C–N achieved in a tandem process. In this carbonylation-etherification cascade process both carbonyl and ethereal oxygen originates from Cs_2CO_3 .