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Copper(I)-catalyzed intramolecular cyclization reaction of 2-(2′-chlorophenyl)ethanol to give 2,3-dihydrobenzofuran

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Abstract

Functionalized 2,3-dihydrobenzofuran can be synthesized in good yield via an intramolecular cyclization of an aryl chloride and a primary alcohol under the catalysis of copper(I) chloride salt.

Keywords: 2-(2′-chlorophenyl)ethanol; intramolecular cyclization; catalysis; copper(I) chloride; 2,3-dihydrobenzofuran.

Several drug candidates in development contain a core structure of a substituted dihydrobenzofuran.[1] A common intermediate in the synthesis of these drugs is 4-vinyl-2,3-dihydrobenzofuran. This compound could be prepared from the 4-halo-2,3-dihydrobenzofuran by known chemistry, such as palladium-catalyzed cross-coupling reactions of aryl halides, e.g. the 'Stille' reaction and the 'Suzuki' reaction, or nickel-catalyzed Grignard cross-coupling reactions. However, there is no method readily available in the literature to synthesize the necessary starting 4-halo-2,3-dihydrobenzofuran.

We reasoned that 2′,6′-dichlorophenylacetic acid, commercially available and inexpensive, should be easily reduced to an alcohol, and the latter could be subjected to an intramolecular cyclization that would give us the desired product. The Ullman reaction, a well-known method for synthesis of aryl ethers, has been widely used in organic synthesis.[2] In general, the Ullman reaction requires an activated aryl iodide or bromide under the catalysis of a copper(I) salt under forcing conditions and in the presence of a large excess of alkoxide.[3] We found no reports on the intramolecular cyclization reaction between an alcohol and aryl chloride. A palladium-catalyzed intramolecular cyclization reaction giving dihydrobenzofuran derivatives has recently been reported.[4] However, the substrates are also restricted to aryl bromides or iodides and secondary or tertiary alcohols. In our case, cyclization of a poorly active aryl chloride and a primary alcohol are required to produce the desired dihydrobenzofuran. Therefore, it was necessary to examine the Ullman reaction for its ability to perform an intramolecular cyclization between an aryl chloride and a primary alcohol. The general reaction is shown in Scheme 1.

2-(2′,6′-Dichlorophenyl)ethanol was prepared by reduction of 2-(2′,6′-dichlorophenyl)acetic acid using a literature procedure.[5] The intramolecular cyclization reaction of 2-(2′,6′-dichlorophenyl)ethanol

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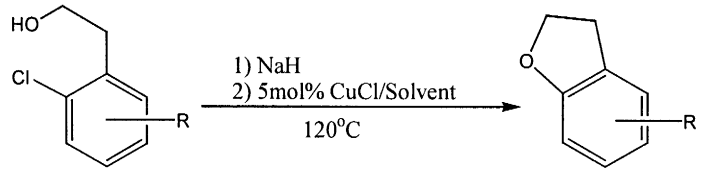


R = H, Cl

Scheme 1.

was first attempted using sodium hydride (1.0–1.25 equiv.) and CuI (0.5 equiv.) in collidine at ~120°C for 2–4 h. After work-up, the crude product isolated was checked by ^{1}H NMR, which indicated only ~50% conversion. Prolonging the reaction or increasing the amount of catalyst to 1.0 equiv. did not improve the conversion. Increasing the amount of sodium hydride to 1.5–2.0 equiv. gave significant impurities, including unknown polyaromatic impurities. Isolation of the product from such a reaction mixture proved to be difficult.

Nevertheless, encouraged by the result that the cyclization reaction occurred to give the desired product, we decided to optimize this novel intramolecular cyclization reaction under the catalysis of a Cu(I) salt. To our knowledge, the choice of copper catalyst for normal Ullman reaction was not critical.[2b] We preferred to use CuCl due to its lower cost. We found that the reaction could be carried out in a wide range of solvents, such as pyridine, collidine, dioxane, toluene and toluene/ethyl acetate,[6] but essentially failed in lutidine. We have also found that the success of this intramolecular cyclization reaction was dependent on the amount of catalyst and base used, as well as the solvent, as can be seen from the data summarized in Table 1.

Table 1
Copper(I)-catalyzed intramolecular cyclization reaction of 2-(2,6-dichlorophenyl)ethanol

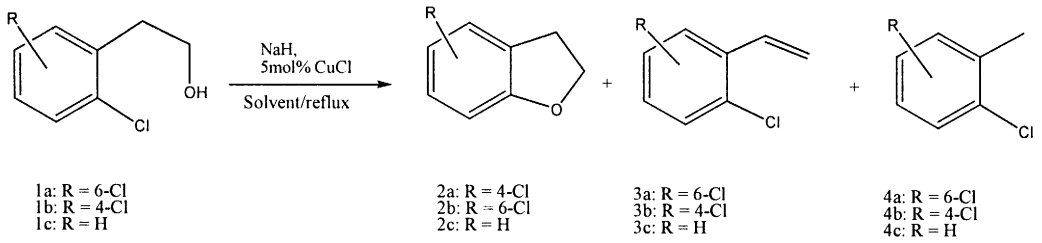
Entry	Reaction conditions		Solvent	Base		Catalyst		Conversion[a] %
	Temp (°C)	Time (hr)		Type	Equiv.	Type	Equiv.	
1[b]	120	2	2,4,6-Collidine	NaH	1.05	CuI	0.5	52.6
2	120	2	2,6-Lutidine	NaH	1.25	CuI	0.5	1.7
3	115	1.5	Pyridine	NaH	1.25	CuI	0.5	65.3
4	115	2	Pyridine	NaH	1.25	CuCl	0.5	55.6
5	115	2	Pyridine	NaH	1.25	CuCl	0.25	74.9
6	115	2	Pyridine	NaH	1.25	CuCl	0.10	85.6
7	**115**	**2**	**Pyridine**	**NaH**	**1.25**	**CuCl**	**0.05**	**92.4**
8	115	2	Pyridine	NaH	1.25	CuCl	0.01	85.9
9	115	2	Pyridine	NaH	1.15	CuCl	0.05	75.9
10	115	2	Pyridine	NaH	1.05	CuCl	0.05	75.1
11	110	4	Toluene	NaH	1.25	CuCl	0.05	45.5
12	102	4	Dioxane	NaH	1.25	CuCl	0.05	69.7
13	110	24	Toluene	NaH	1.25	CuCl	0.05	81.4
14	**110**	**24**	**Toluene/EtOAc**	**NaH**	**1.25**	**CuCl**	**0.05**	**90.7**
15	102	24	Dioxane	K_2CO_3	1.25	CuCl	0.05	0
16	107	2	Pyridine	NaOMe	1.25	CuCl	0.05	18.2

a. Conversion was determined by ^{1}HNMR and/or GC.
b. Reaction run at 10% (w/v) concentration versus 5% (w/v) for all other reactions

It was found that CuCl worked as well as CuI. It is interesting to note that when the amount of catalyst was reduced, the yield increased (entries 4–8). The optimal amount of the catalyst was found to be ~5 mol%. It can be seen from Table 1 (entries 7 and 14) that the reaction carried out in pyridine or toluene (with 5 mol% ethyl acetate) gave the highest conversion (91–92%). It is also worth noting that

no intermolecular Ullman reaction occurred when sodium methoxide was used as a base (entry 16), indicating that intramolecular cyclization is much more favorable than intermolecular reaction.

Although a high yield was achieved by using 5 mol% CuCl in pyridine, two major impurities (1–4.5%) were identified after analyzing the product profile by ^{1}H NMR, ^{13}C NMR and GC/MS. These were 2,6-dichlorostyrene and 2,6-dichlorotoluene (Scheme 2). 2,6-Dichlorotoluene was at a relatively low level and was easy to remove by distillation. However, the 2,6-dichlorostyrene was difficult to separate from the product by simple distillation and thus had to be held to as low a level as possible.[7]



1a: R = 6-Cl
1b: R = 4-Cl
1c: R = H

2a: R = 4-Cl
2b: R = 6-Cl
2c: R = H

3a: R = 6-Cl
3b: R = 4-Cl
3c: R = H

4a: R = 6-Cl
4b: R = 4-Cl
4c: R = H

Scheme 2.

Only a few substrates were available for a study of the generality of this intramolecular cyclization reaction. It was found that reaction can not only proceed with dichloro substitution on the benzene-ring, but also with monochloro substitution. The results are summarized in Table 2.

Table 2
Copper(I) chloride-catalyzed intramolecular cyclization reaction[8]

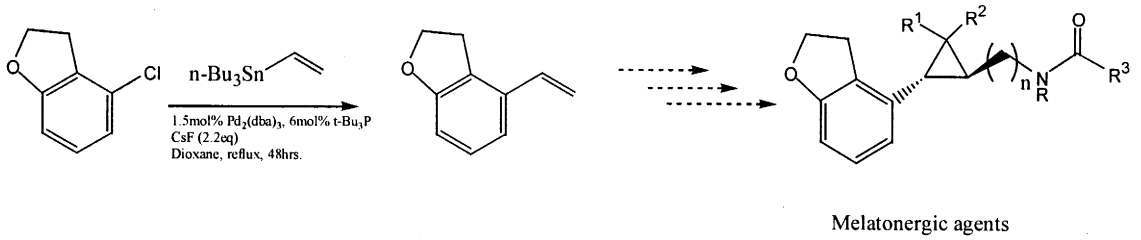
Entry	Substrate	Solvent	Time (hr.)	Conversion %	Yield[1] %	Selectivity (%)		
						2a-c	3a-c	4a-c
1	1a	Pyridine	2	94.9	77.4	91.9	5.3	2.8
2	1a	Toluene[2]	24	99.7	89.5	99.3	trace	0.7
3	1b	Pyridine	4	92.0	63.0	74.4	22.1	3.6
4	1b	Toluene[2]	24	97.6	76.9	92.8	1.2	6.0
5	1c	Pyridine	4	74.5	47.1	72.8	23.5	3.7
6	1c	Toluene[2]	24	93.0	73.6	95.5	0.3	3.2

1. G.C. yield after usual work-up. The work-up procedure was not fully optimized.
2. with 5mol% EtOAc added.

It can be seen from Table 2 that toluene with 5 mol% ethyl acetate is clearly the preferred solvent to use. Although the reaction is faster in pyridine, the selectivity of forming the desired product is poorer. For example, the reaction of 2-(2′,4′-dichlorophenyl)ethanol in pyridine (entry 3) gave a reasonable conversion, but 2,4-dichlorostyrene **3b**, a byproduct, became rather significant with ~22% selectivity. In toluene/ethyl acetate, the product selectivity increased to ~93% with the formation of only a small amount of impurities. A similar phenomenon was also observed with other substrates. It can be concluded that toluene/ethyl acetate gives a slower reaction, but higher selectivity for the formation of the desired product. In addition, from a manufacturing point of view, the use of toluene is more attractive than pyridine in view of its lower toxicity, lower cost and ease of recovery.

To demonstrate the practical utilization of 4-chloro-2,3-dihydrobenzofuran in our synthesis, the substrate was subjected to the palladium-catalyzed ‘Stille’ cross-coupling reaction, which was recently developed by Fu and Littke,[9] with tributylvinyltin in the presence of 2 equiv. CsF and this gave 4-vinyl-2,3-dihydrobenzofuran in a yield of ~58%. The latter can then be converted into useful melatonergic agents via a multiple-step synthesis (Scheme 3).[1]

In conclusion, we have developed an efficient method for the synthesis of 2,3-dihydrobenzofuran derivatives via a novel intramolecular cyclization of a poorly active aryl chloride and a primary



Scheme 3.

alcohol under the catalysis of copper(I) chloride. We believe that recent advancements made in activating aryl chlorides under transition-metal catalysis can provide a useful tool to further elaborate chlorodihydrobenzofurans.[10]

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7. This was accomplished by changing the solvent from pyridine to toluene with 5 mol% ethyl acetate. Details can be seen in Table 2.
8. A typical procedure: To a dry, 100 mL, three-necked, round-bottomed flask equipped with condenser, thermocouple, and stir bar was added 2,6-dichlorophenyl ethanol (1.0 g, 5.23 mmol) with toluene (12 mL). To the flask was then added NaH (0.165 g, 6.54 mmol, 1.25 equiv.) with toluene (4 mL). The reaction mixture was heated at 40°C for 15 min before cooling to room temperature. Then CuCl (0.026 g, 0.26 mmol, 0.05 equiv.) was added with toluene (4 mL) and EtOAc (0.03 g, 0.26 mmol, 0.05 equiv.). The reaction mixture was again heated at reflux for 24 h. The reaction mixture was cooled to room temperature, quenched with water (20 mL), filtered over Celite and the cake was washed with MTBE. The aqueous layer was separated and extracted with 2×25 ml MTBE. The combined organic layers were then washed with 100 mL 1N HCl followed by 2×100 mL portions of saturated $NaHCO_3$ solution and 100 mL saturated NaCl solution. The final solution was dried with anhydrous sodium sulfate before being concentrated under reduced pressure to give ~0.7 g product, yield 88%.
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