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A Simple and Efficient Access to Naphtho[*b*]furans by Claisen Rearrangement/Cyclization of Bromonaphthyl 3-Phenylallyl Ethers

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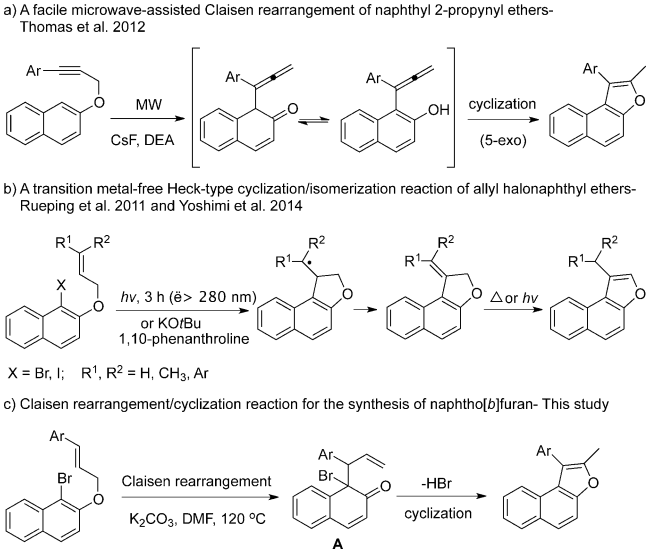
Abstract: A transition-metal-free Claisen rearrangement/cyclization reaction was developed for the synthesis of naphthofuran derivatives from bromonaphthyl 3-phenylallyl ethers. The nature of the base employed in this reaction plays an important role in determining the ratio for the formation of naphthofuran and naphthol products. By using K_2CO_3 as base and DMF as solvent, we have synthesized a variety of functionalized naphthofurans in good to high yields (49–92%) and with satisfactory selectivities.

Keywords: bromonaphthyl ethers; Claisen rearrangement; cyclization; naphthofurans; transition-metal-free

Naphtho[*b*]furans are important structural motifs that find presence in many natural products[1] and pharmaceutical agents.[2] As a consequence, numerous efficient synthetic strategies have been developed for the construction of this structure. Among the protocols reported to date, most involve the use of versatile starting substrates[3] in combination with a suitable transition-metal catalyst, such as Pd,[4] Pt,[5] In,[6] Ru,[7] Au,[8] Ag,[9] Fe,[10] Cu.[11] Despite of their synthetic versatility, the cost of transition-metal catalysts and the difficulty associated with removing transition-metal impurities from final products may restrict the practical applicability of these methods.

Not surprisingly, transition-metal-free approaches to prepare naphthofurans have also been pursued. For example, in 2012, Thomas et al.[12] reported that naphtho[*b*]furans could be obtained in high yields by a facile microwave-assisted Claisen rearrangement of naphthyl 2-propynyl ethers (Scheme 1a). Unfortunately, expensive and highly hygroscopic CsF was used as base to promote this reaction. More recently, Rueping[13] and Yoshimi et al.[14] prepared a series of naphtho[*b*]furans in good yields, utilizing a transition-metal-free Heck-type cyclization/isomerization reaction of halonaphthyl ethers (Scheme 1b). However, these transformations required either highly basic KO*t*Bu or UV light, thus limiting their functional group tolerance. Therefore, the development of a simple, straightforward and cost-effective method to synthesize naphtho[*b*]furans is highly desirable. Herein, we report a transition metal-free process for the synthesis of naphtho[*b*]furans from bromonaphth-



Scheme 1. General strategies for the construction of the naphtho[*b*]furan skeleton through a transition-metal-free system.

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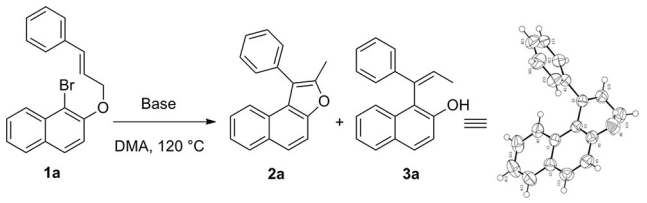
Table 1. Effect of bases on this reaction[a]



Entry	Base	Yield of **2a** [%][b]	Yield of **3a** [%][b]
1	–	0	0
2	NaOAc	23	43
3	Li_2CO_3	28	49
4	Na_2CO_3	45	47
5	K_2CO_3	85	11
6	Cs_2CO_3	68	24
7	K_3PO_4	66	27
8	NaOH	22	49
9	LiO*t*Bu	62	27
10	NaO*t*Bu	4	93
11	KO*t*Bu	26	46

[a] Reaction conditions: **1a** (0.25 mmol), base (0.5 mmol), DMA (1 mL), under nitrogen, 120 °C, 24 h.
[b] Yields are determined by HPLC.

Table 2. Effect of solvents on this reaction[a]

Entry	K_2CO_3 [mmol]	Solvent	Temp [°C]	Yield of **2a** [%][b]	Yield of **3a** [%][b]
1	0.5	toluene	100	2	20
2	0.5	*n*-butanol	100	13	5
3	0.5	1,4-dioxane	100	1	2
4	0.5	NMP	120	58	40
5	0.5	DMA	120	85	11
6	0.5	DMF	120	89	8
7	0.5	DMF	100	24	2
8[c]	0.5	DMF	100	71	6
9[c]	0.5	DMF	80	11	8
10	0.25	DMF	120	84	8
11	0.75	DMF	120	91	7
12	1.0	DMF	120	86	8

[a] Reaction conditions: **1a** (0.25 mmol), under nitrogen, solvent (1 mL), 8 h.
[b] Yields are determined by HPLC.
[c] 24 h.

yl 3-phenylallyl ethers *via* a Claisen rearrangement/cyclization cascade event (Scheme 1c). This method requires K_2CO_3 as base and DMF as solvent, and provides various naphtho[*b*]furan compounds with diverse substitution patterns.

In our initial studies, 1-bromo-2-[[(2*E*)-3-phenyl-2-propen-1-yl]oxy]naphthalene (**1a**) was chosen as model substrate and dimethylacetamide (DMA) as solvent (Table 1). However, no desired naphtho[2,1-*b*]furan **2a** was detected after being heated at 120 °C for 24 h (Table 1, entry 1). Considering there is a formal loss of HBr during the product formation, we envisioned that a base would be a good promoter for the reaction. As expected, the introduction of bases like NaOAc, Li_2CO_3, or Na_2CO_3 induces this reaction to occur, and the desired product **2a** was obtained in acceptable yields (Table 1, entries 2–4). It is noteworthy that under these conditions, a byproduct, 2-naphthol derivative **3a** was also formed in significant amounts (43–49 % yields), the structure of which was unambiguously confirmed by single-crystal X-ray diffraction.[15,16] Further screening of base showed K_2CO_3 to be optimal, which not only suppressed the formation of **3a**, but afforded **2a** in 85 % yield (Table 1, entries 5–11). Interestingly, the use of sodium *tert*-butoxide (NaO*t*Bu) led to **3a** as the major product in 93 % yield (Table 1, entry 10). These results suggest that the base exhibits a dramatic effect on both reaction selectivity and yield.

Having identified the optimal base, we then screened different solvents (Table 2). The use of toluene, *n*-butanol, 1,4-dioxane, or *N*-methylpyrrolidone (NMP) significantly decreased the yield (Table 2, entries 1–4). Switching solvent to dimethylformamide (DMF) improved the reaction efficiency, and the desired naphtho[*b*]furan **2a** was formed in 89 % yield (Table 2, entry 6). Lowering the reaction temperature had a deleterious effect on the reaction performance (Table 2, entries 8 and 9). The amount of K_2CO_3 was also briefly assessed. The best yield of **2a** was observed when 3 equiv of K_2CO_3 was employed (Table 2, entries 10–12). Based on these optimization studies, further reactions were performed in DMF at 120 °C in the presence of 3 equiv of K_2CO_3.

To evaluate the substrate scope of this reaction, we subjected a wide range of bromonaphthyl 3-phenylallyl ethers to the established conditions. First, different substituents on the 3-phenyl moiety were tested (Table 3). Among the different *para*-substituted phenyl derivatives screened, those bearing electron-donating groups provided higher product yields than those bearing electron-withdrawing groups (Table 3, **2b–2g**). Furthermore, the yields of the byproducts 2-naphthol **3c-3e** decreased as the substituent became more electron-donating. To our delight, *meta*- or sterically demanding *ortho*-substituted phenyl derivatives were also tolerated, furnishing the desired products **2h–2l** in good to excellent yields (79–88 %). The structure of compound **2k** was further confirmed by single-crystal X-ray diffraction.[17] Notably, the isomeric 2-bromonaphthyl ether (**1a′**) also participated in this reaction, and gave naphthofuran **2a′** in 53 % yield. Unexpectedly, for substrate **1m** bearing a 2-CF_3 group, a double bond isomerization occurred to give vinyl ether **1m′** in 50 % yield,[18] and none of the desired product was observed.

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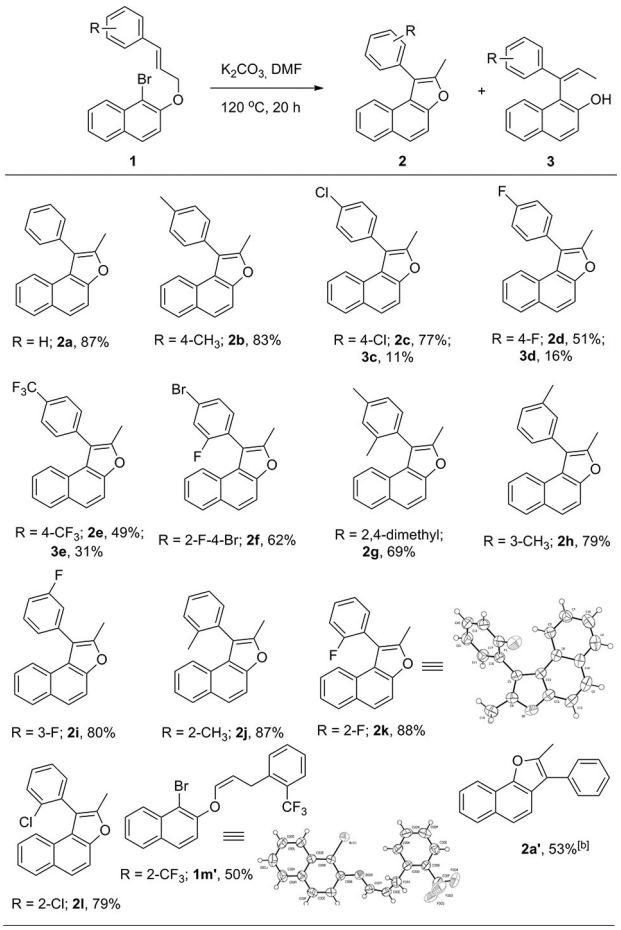
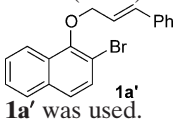
Table 3. Scope of the transition-metal-free Claisen rearrangement/cyclization reaction of 1-bromonaphthyl derivatives.[a]

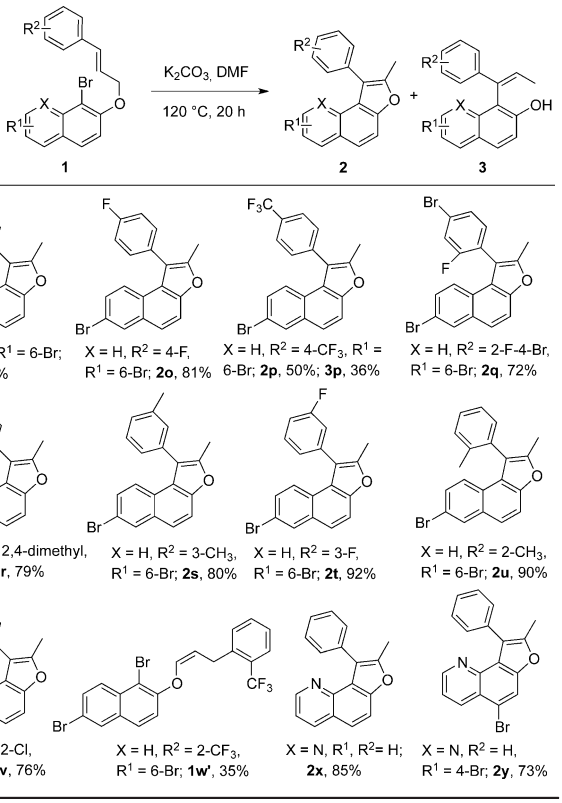


[a] Reaction conditions: **1** (0.25 mmol), K_2CO_3 (0.75 mmol), DMF (1 mL). Yields of isolated products.



[b] **1a′** was used.

Table 4. Scope of the transition-metal-free Claisen rearrangement/cyclization reaction of 1,6-dibromonaphthyl derivatives.[a]



[a] Reaction conditions: **1** (0.25 mmol), K_2CO_3 (0.75 mmol), DMF (1 mL). Yields of isolated products.

We next explored the reactivity of 1,6-dibromonaphthyl ethers under the same reaction conditions (Table 4). To our delight, all the tested substrates **1n–1v** could react smoothly, affording corresponding brominated naphtho[*b*]furans **2n–2v** in up to 92% yield. Interestingly, only one C–Br bond was chemoselectively cleaved during the reaction, and the remaining aryl bromide functional group can serve as a versatile handle for further manipulation. In case of substrate **1w** containing 2-CF_3 group at 2-propenyl moiety, no desired product was formed. Like **1m** it was again prone to undergo double bond isomerization into the vinyl ether compound **1w′**.[19] These observations could be explained by an intramolecular [1,3]-type H-shift.[10d,13] In addition, substrates bearing pharmaceutically relevant quinoline rings could also be used in this reacting, resulted in **2x** and **2y** in good to excellent yields. These results demonstrated the generality and usefulness of this strategy.

We have performed several experiments to elucidate the mechanism of this transformation (Table 5). To rule out the possibility that this reaction was catalyzed by the trace level of transition-metal contaminant,[20] we repeated our model reaction (**1a** to **2a**, Table 5, entry 1) using metal-free, high purity (99.997%) K_2CO_3.[21] No reduction in rate or change in selectivity was observed in this case (Table 5, entry 1).

We then preformed this reaction in the presence of air or radical inhibitor 2,2,6,6-tetramethyl-1-piperidinoxy (TEMPO). The reaction efficiency was not significantly inhibited under these conditions (Table 5, entries 2 and 3). Moreover, the reaction worked equally well when conducted in the dark (Table 5, entry 4). These results described above suggested that a radical mechanism[13,14] might not be operating in this process. Furthermore, chloro-substituted derivative **1aa** produced the desired product **2a** only in 6% yield under the present reaction conditions, whereas the use of higher temperature afforded **2a** in 36% yield. (Y = Cl, Table 5, entries 5 and 6). Here, a plausi-

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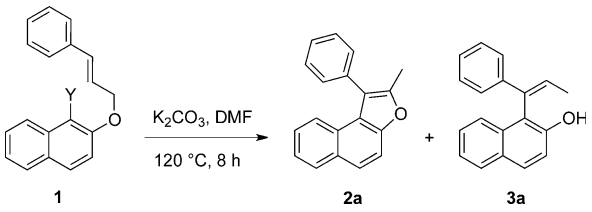
Table 5. Condition-controlled Claisen rearrangement/cyclization reaction of **1**[a]

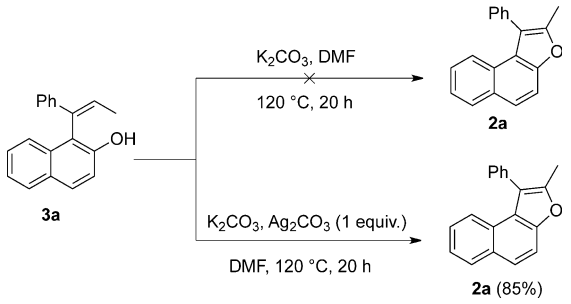


Entry	Y	Conditions	Yield of **2a** [%][b]	Yield of **3a** [%][b]
1	Br	K_2CO_3(99.997%, Alfa), N_2	86	8
2	Br	air	73	17
3	Br	TEMPO, N_2	67	31
4	Br	no light, N_2	89	7
5	Cl	N_2	6	5
6[c]	Cl	N_2	36	46

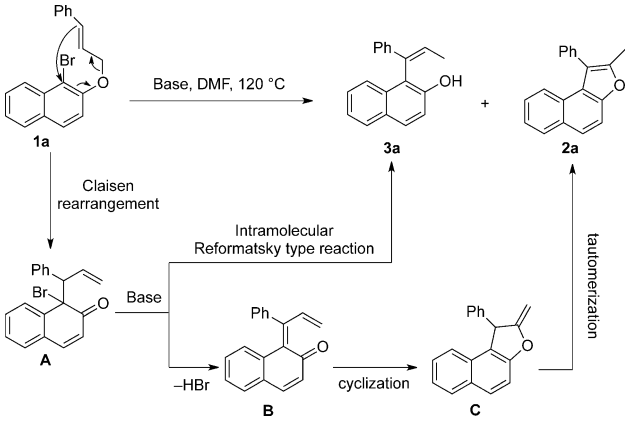
[a] Reaction conditions: **1** (0.25 mmol), K_2CO_3 (0.75 mmol), DMF (1 mL), 120 °C, 8 h.
[b] Yields are determined by HPLC.
[c] 140 °C, 20 h.

ble explanation could be a lower compulsion of the chlorine to leave the naphthyl ring, which hinders the processes of Claisen rearrangement and cyclization.[13] Additionally, it was found that **3a** failed to give any of the desired product **2a** under the employed conditions, so **3a** was not the intermediate species to form **2a**. Addition of Ag_2CO_3 led to the transformation of **3a** to **2a** in high yield (Scheme 2).

On the basis of these results, a tentative mechanism of this reaction is proposed in Scheme 3. Phenylallyl ether **1a** first undergoes a [3,3]-sigmatropic rearrangement to give the dearomatized intermediate **A**. Base-induced dehydrohalogenation of **A** then affords alkenyl ketone **B**, which then cyclizes to give the aromatized intermediate **C**.[12,22] The desired product **2a** is ultimately constructed *via* tautomerization of **C**,[12,14] another aromatizing process. The byproduct naphthol **3a** is possibly produced by direct reduction of the intermediate **A** by base or solvent.[23] Further study on the formation of **3a** is currently ongoing in our laboratory and will be reported in due course.



Scheme 2. Further studies to understand the mechanism.



Scheme 3. Proposed mechanism.

In conclusion, we have developed a simple and efficient method for constructing various naphtho[*b*]furans from bromonaphthyl 3-phenylallyl ethers *via* a transition-metal-free Claisen rearrangement and cyclization reaction. Compared with the previous approaches, the present methodology has the advantages of simple reaction system, operational ease, and broad applicability, and should be an attractive choice for the synthesis of naphtho[*b*]furan derivatives.

Experimental Section

Representative procedure for 2a: K_2CO_3 (0.75 mmol) and **1a** (0.5 mmol) were added into a dried Schlenk tube with a magnetic bar, which was subjected to evacuation/flushing with dry nitrogen five times, and then DMF (1.0 mL) was added into it. The reaction mixture was heated at 120 °C for 20 h with stirring. After cooling, water (3 mL) was added into the mixture and subsequently the mixture was extracted with ethyl acetate (3×3 mL). The combined organic extracts were washed with brine (3×3 mL), dried with anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by silica gel chromatography (petroleum ether) to give the product **2a** (112 mg, 0.435 mmol, 87%).

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[18] See the Supporting Information. CCDC-1036080 contains the supplementary crystallographic data for **1m′**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[19] See the Supporting Information. CCDC-1036081 contains the supplementary crystallographic data for **1w′**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
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