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A Novel Base-Promoted Cyclization: Synthesis of Substituted Benzo[b]furans

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Abstract

A new base-promoted cyclization for the synthesis of substituted benzo[b]furans is described. This method is simple and inexpensive and gives good yields.

Benzo[*b*]furan is an important structural scaffold in pharmaceutical research because compounds containing this moiety show a wide range of pharmacological activities.^{1–4} For example, the benzofuran moiety is found in antidepressant (–)-BPAP,⁵ angiotensin II inhibitors,⁶ 5-lipoxygenase inhibitors,⁶ neurokinin-2 receptor antagonist,⁷ cathepsin K inhibitors,³ and calcium entry blockers. In addition, there are also many benzofuran-containing natural products including (–)-concentricolide,⁸ (+)-frondosin B⁹ and the eupomatoid family.¹⁰ Therefore, there is a very high level of interest in finding efficient ways of constructing the benzo[*b*]furan core structure.

(–)-Concentricolide

Frondosin B

Several approaches have been reported in the literatures.^{11–15} Most recent approaches have focused on the use of transition-metal catalyzed synthesis of benzo[*b*]furan compounds^{16, 17} including metal-catalyzed, one-pot synthesis from 2-halophenols and terminal^{18, 19} or internal alkynes²⁰ by Sonogashira coupling²¹ followed by cyclization and transition metal catalyzed heteroannulation of 2-alkynyl phenols or 2-alkynylphenol ethers.²² In most published literature, the synthesis of benzo[*b*]furans is via tandem Sonogashira coupling/5-endo-dig cyclization using a palladium catalyst or copper salt²⁶ and oxidative pathway.²⁷

However, most of these approaches require expensive metal reagents, harsh reaction conditions and have limited functional group tolerance. Herein, we describe a new base-promoted synthesis of 2-substituted benzo[*b*]furans from heteroannulation of 2-

alkynylphenols. In the present work, heating a mixture of **1a** and NaN₃ in the presence of CuI in DMF at 60 °C led to the unexpected formation of compound **2a** as the major product. Further examinations of the reaction conditions found that CuI was not necessary for the reaction. Thus we suspected that deprotonation of the phenol hydroxyl group by a base was probably the driving force for the reaction. With this in mind, we screened this reaction under different conditions by altering the base used and found that Cs₂CO₃ was the most effective and Et₃N was ineffective in catalyzing the reaction (Table 1). With such results we concluded that in the original reaction, NaN₃ was acting merely as a base.

In order to explore the scope of this cyclization reaction, we were interested in examining the effect of various substituents on the reaction. The study started with the preparation of substituted phenols **1a-d**. These compounds (**1a-d**) were subjected to the ring closure reaction conditions (60 °C in dry DMF, Cs₂CO₃). Substituted benzo[b]furans with different functional groups were synthesized in good yields (76-88%, Table 2). Especially worth mentioning is the synthesis 5-nitrobenzo[b]furan. It is well known that isomers form under direct nitration of benzo[b]furan,²³ so most nitrobenzo[b]furans are synthesized via intramolecular condensation of suitably substituted nitrobenzenes.²⁴ Thus far, only a few metal-catalyzed heteroannulation techniques have been applied to the synthesis of nitrobenzo[b]furan. Since the nitro group is sensitive to strong basic conditions at high temperature, many approaches to the synthesis of benzo[b]furans have proven too harsh for the nitro substituents.²⁵ So the smooth cyclization method described here should be very useful.

Having successfully prepared a range of benzofuran-2-carboxylate (**2a-d**), we extend this methodology to the synthesis of 2-substitued benzo[b]furans from *o*-alkynylphenol. For optimization of the cyclization reactions, we chose compound **3a** and screened different solvents and temperatures. The data (Table 3) revealed that DMF is the best solvent for cyclization.

In most published literature, the synthesis of benzo[b]furans is via tandem Sonogashira coupling/5-endo-dig cyclization using a palladium catalyst or copper salt²⁶ and oxidative pathway.²⁷ Using our protocol, we were able to cyclize *o*-alkynylphenols (**3a-m**) to the corresponding benzo[b]furans (**4a-m**) in moderate to good yields (Table 4). It should be noted that many of the same cyclizations, such as **4a**, **4c**²⁸ and **4d**,²⁹ have been noted under Pd catalysis. Our results suggest that metal catalysis is not necessary in some of the literature procedures.

In conclusion, we have reported a new base-promoted synthesis of benzo[b]furans with good yields. This method can be applied to the synthesis of the 5-nitrobenzofuran, which is difficult to produce using to other methods. This synthetic route is palladium/copper free and avoids the use of expensive or air sensitive reagents and represents a novel method for the easy synthesis of benzofurans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Base promoted cyclization of 1a

Entry	Solvent	Base	Yield (%)
1	DMF	K ₂ CO ₃	78
2	DMF	TEA	NR
3	DMF	DIPEA	NR
4	DMF	Cs ₂ CO ₃	86
5	DMF	NaCN	75
6	DMF	DBU	75
7	DMF	TEA+DMAP	79

Table 2
Base promoted cyclization of 1a-d^a

Entry	Phenol	Benzofuran	Yield (%) ^b
1	1a	2a	86
2	1b	2b	76
3	1c	2c	88
4	1d	2d	85

^aStandard reaction conditions: 1eq. of **1**, 2eq. of CS₂CO₃ in dry DMF at 60 °C

^bIsolated yields

Table 3
Base promoted cyclization of 3a

Entry	Solvent	T °C	Yield (%)
1	DMF	60	82
2	DMF	RT	NR
3	CH ₃ CN	60	45
4	MeOH	60	NR
5	DMSO	60	66
6	1,4-Dioxane	60	NR

Table 4
Base promoted cyclization of 3a-m^a

Entry	Phenol	Benzofuran	Yield (%) ^b
1	3a	4a	82
2	3b	4b	86
3	3c	4c	90
4	3d	4d	82
5	3e	4e	78
6	3f	4f	84
7	3g	4g	91
8	3h	4h	83

Entry	Phenol	Benzofuran	Yield (%) ^b
9			85
10			92
11			86
12			79
13			84

^aStandard reaction conditions: 1eq. of **1**, 2eq. of Cs₂CO₃ in dry DMF at 60 °C

^bIsolated yields