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tert-BuOK-mediated carbanion–yne intramolecular cyclization: synthesis of 2-substituted 3-benzylbenzofurans

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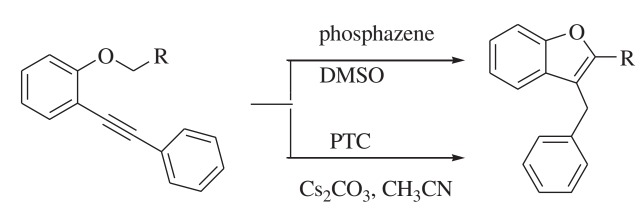
A mild, efficient, and regioselective carbanion–yne intramolecular cyclization mediated by *t*-BuOK for the synthesis of 2-substituted 3-benzylbenzofurans is developed. It was started from *o*-iodophenol (**1**), based on O-alkylation, and the Sonogashira reaction in sequence to produce 2-(2-phenylethynylphenoxy)-1-arylalkanones (**5**). An intramolecular carbanion–yne 5-*exo-dig* cyclization reaction of **5**, which was mediated by *t*-BuOK, yielded title benzofurans in good yields.

1. Introduction

The carbon–carbon bond formation, an important synthetic strategy for constructing various benzocarbocyclic and benzoheterocyclic compounds, has been well documented in literatures. For instance, strategies for intramolecular carbon–carbon bond formation which mainly reported were the intramolecular Heck reaction for medium-sized oxa-heterocycles,[1] for including coumarins,[2] tetrahydroanthracenes,[3] as well as others.[4] Because benzofurans exhibited diverse biological activities, such as antibacterial and antifungal,[5] antitumor and antiviral,[6] anticonvulsant and anti-inflammatory,[7] and antileishmanial activity,[8] the development of a mild, diverse, efficient, and practical route for the synthesis of benzofuranoides is requisite and significant from the view-points of synthetic and medicinal chemistry. Up to present various approaches for the synthesis of benzofuran, such as palladium-catalyzed enolate arylation with *o*-bromophenols,[9] palladium-catalyzed reactions of propargylic carbonates with nucleophiles,[10] a one-pot sequential Sonogashira coupling,[11] and ring-closing metathesis[12] have been disclosed. Recently, Terada, et al.[13a] developed an excellent method using phosphazene base-catalyzed an intramolecular carbon–carbon bond cyclization in DMSO (dimethyl sulfoxide) for the synthesis of 2-substitued 3-benzylbenzofurans and Hu et al.[13b] also reported the similar strategy for benzofurans using phase-transfer-catalyzed methodology (Scheme 1).



Scheme 1. Intramolecular cyclization of *o*-alkynylphenyl ether mediated by phosphazene[13a] or PTC/cesium carbonate[13b] to generate benzofuran.

However, those methods described above have encountered some disadvantages. Such as, phosphazene used by Terada's method as reaction base is complicated in structure and very expensive in price and DMSO utilized as reaction solvent is a high boiling point solvent and is difficult to remove. Moreover, the selected PTC (phase transfer catalyst) and base for cyclization reported by Hu et al. to yield benzofurans, which is variable with reaction condition and lacking of straightforward, are disadvantages. Moreover those reported methods to prepare benzofurans with limited substituents and insufficient investigation for insight into this carbanion–yne cyclization are drawbacks. Recently we have successfully reported a carbanion–olefin cyclization which mediated by potassium *tert*-butoxide for diverse chroman derivatives (Scheme 2).[14]

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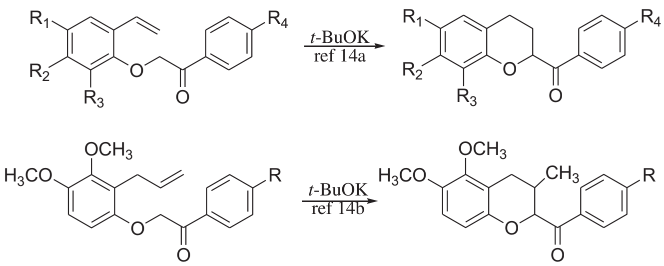
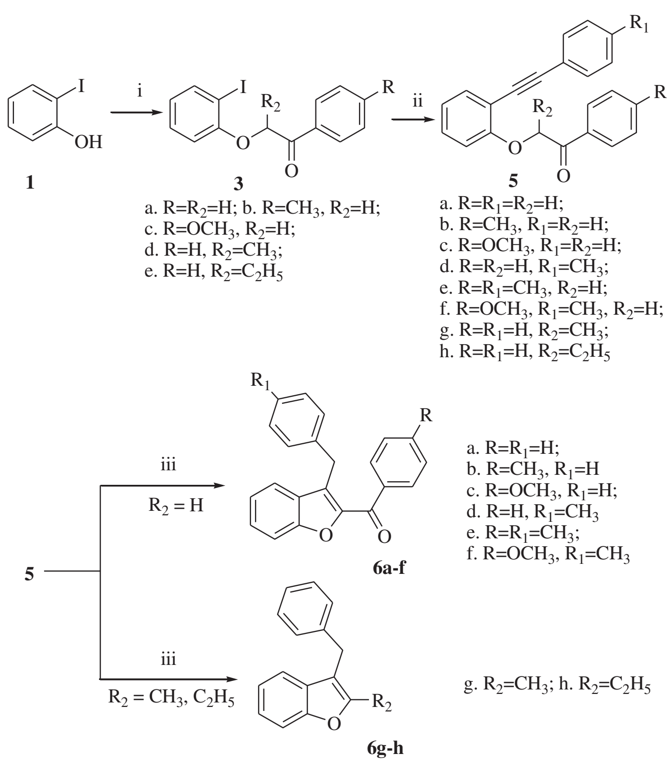


Scheme 2. Carbanion–olefin cyclization mediated by potassium *tert*-butoxide to yield chroman derivatives.

In these studies we found both 2-phenylvinylphenoxy and 2-phenylallylphenoxy intermediates could be, respectively, mediated by potassium *tert*-butoxide to undergo carbanion–olefin intramolecular 6-*endo-trig* cyclization with regiospecificity to yield chroman derivatives. Thus, we would like to extend our previous studies to investigate the cyclization of carbanion–yne mediated by potassium *tert*-butoxide. Herein, we report the result to build up various 2-substituted 3-benzylbenzofurans from intramolecular carbanion–yne 5-*exo-dig* cyclization by two different pathways, which briefly mediated by potassium *tert*-butoxide (Scheme 3).

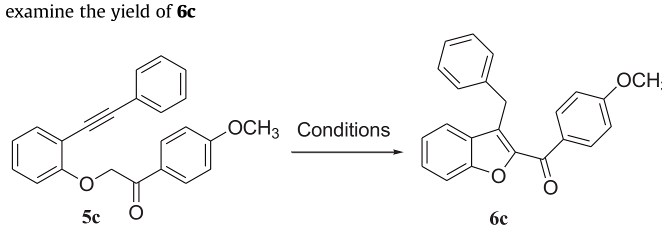


Scheme 3. Intramolecular carbanion–yne 5-*exo-dig* type cyclization reaction mediated by *t*-BuOK to generate 2-aroyl-3-benzylbenzofurans. Reagents and reaction condition: (i) 2-bromoacetophenones (**2a–e**), K_2CO_3, acetone, reflux 2–3 h, 87–91%; (ii) $Pd(PPh_3)_2Cl_2$, CuI, phenylacetylene (**4a**), *p*-methylphenylacetylene (**4b**), $(^iPr)_2NH$, THF, reflux 3 h, 76–84%; (iii) *t*-BuOK, THF, reflux 0.5 h, 80–88%.

2. Results and discussion

As a general procedure, the reaction of *o*-iodophenol (**1**) with 2-bromoacetophenones (**2a–e**) in the presence of K_2CO_3 afforded 2-(2-iodophenoxy)arylethanones (**3a–e**) in yields of 87–91%. The typical absorption of IR at 1673–1698 cm^{-1} exhibited the presence of C=O group in the molecules of **3a–e**, and the methylene protons with singlet signals at δ 5.24–5.32 in ^1H NMR were commonly found in the structure **3a–c**. The elucidation of structures **3d–e** are as follows. In ^1H-NMR spectrum, a doublet methyl signal with coupling constant J=6.8 Hz at δ 1.80 and a quartet one-proton signal with coupling constant J=6.8 Hz at δ 5.39 indicating the presence of $-CH(CH_3)CO-$ group were found in **3d**. A triplet methyl signal with coupling constant J=8.0 Hz at δ 1.20, a multiplet two-protons signal at δ 2.17, and a double doublet one-proton signal with coupling constant J=8.0, 4.8 Hz at δ 5.16 indicating the presence of $-CH(CH_2CH_3)CO-$ group were found in **3e**. The selected ^1H NMR spectral data described above are consistent with the data required for **3a–e**. Other spectral data including IR, ^1H NMR, ^{13}C NMR, EIMS, and EA are all equally matched with the data needed for **3a–e**. Then, compound **3** was, respectively, allowed to react with phenylacetylene (**4a**), and *p*-methylphenylacetylene (**4b**), in the presence of CuI, $Pd(PPh_3)_2Cl_2$, and diisopropylamine to undergo the Sonogashira reaction[15] to give 2-(2-phenylethynylphenoxy)-1-arylethanones (**5a–h**) in 76–84% yields. The appearance of C–C triple bond at 2216–2218 cm^{-1} and carbonyl group at 1692–1703 cm^{-1} in the spectra of IR in **5a–h** indicated the successful work of the Sonogashira reaction. Spectral data, such as ^1H NMR, ^{13}C NMR, EIMS, HRMS, and EA are all consistent with the data required for **5a–h**. In order to figure out the optimized reaction of base-mediated the carbanion–yne cyclization, compound **5c** was utilized as model to react with various bases and under various conditions. The results obtained were depicted in Table 1.

Table 1
Treatment of **5c** with various bases (1.2 equiv), solvents (10 mL), and temperature to examine the yield of **6c**



Entry	Base	Solvent	Temp (°C)	Time[a] (h)	Yield[b] (%)
1	*t*-BuOK	THF	rt	1.5	80
2	*t*-BuOK	THF	Reflux	0.5	88
3	*t*-BuOK	CH_2Cl_2	Reflux	1.5	76
4	*t*-BuOK	*t*-BuOH	Reflux	1	82
5	NaOEt	EtOH	rt	3	33[c]
6	NaOEt	THF	rt	4	47[c]
7	$NaNH_2$	THF	rt	4	51

[a] Determined by monitoring the consumption of starting material with TLC.
[b] Isolated by column chromatography.
[c] Recovery of starting material.

From the experimental results obtained at Table 1, we found that compound **5c** can be briefly and efficiently cyclized using *t*-BuOK in refluxing THF (entry 2) to yield benzofurans with regioselectivity and in high yields (80–88%), via an intramolecular 5-*exo-dig* carbanion–yne cyclization. In monitoring by TLC, we found when sodium amide was used as base to give not only the desired product but also other unidentified by-products in this cyclization. When sodium ethoxide was used as base, the longer reaction time and lower yield than that of *t*-BuOK were found (entries 5 and 6). Thus, in this cyclization, the trend of base in the reactivity in THF is potassium *tert*-butoxide>sodium amide>sodium ethoxide (entries 1, 6, and 7). Meanwhile the trend of solvent for this cyclization is THF>*t*-BuOH>CH_2Cl_2 (entries 2, 3, and 4). Therefore, the cyclization of 2-(2-phenylethynylphenoxy)-1-arylethanones (**5a–f**) to yield a series of 2-aroyl-3-benzylbenzofurans (**6a–f**) is achieved using the optimum condition (*t*-BuOK in refluxing THF), which obtained from our experimental results. The chemical structures of