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Selective cyclization of alkynols and alkynylamines catalyzed by potassium *tert*-butoxide

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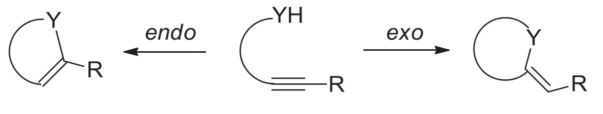
ABSTRACT

Potassium *tert*-butoxide (*t*-BuOK) was found to be an effective catalyst for the cyclization of aromatic alkynols and alkynylamines. In the presence of 10 mol % *t*-BuOK, a range of alkynols were converted to the corresponding *exo*-cyclic enol ethers as pure *Z*-stereoisomers with 100% selectivity and moderate to excellent yields. Moreover, the cyclization of alkynylamines was also achieved to afford indoles and isoindolin-1-ones in good yields.

1. Introduction

Heteroatom-containing compounds are useful building blocks for synthesizing a diverse range of natural products with biological activity.[1] The intramolecular addition of heteroatom–hydrogen bonds across the carbon–carbon triple bond provides a straightforward approach to heterocyclics with 100% atom efficiency, fulfilling the requirements of green chemistry.[2] For example, alkynols and alkynylamines, which are important synthons for numerous structurally fascinating heterocyclic compounds,[3] can undergo cycloisomerization to yield *exo*- or *endo*-heterocycles containing O or N (Scheme 1).[4] *endo*-Cyclization of alkynols has been achieved using Mo, W,[5] Ru,[6] Rh,[7] Ag, Pd and Au complexes or salts[8] as catalysts. Recently, *endo*-iodocyclization of alcohols has also been developed in the presence of $I_2/NaHCO_3$.[9] *endo*-Cyclization of alkynylamines generating indoles, dihydroisoquinolines and dihydroquinolines has also been achieved with diverse catalysts: Cr, Mo, W,[10] Rh,[11] Pd,[12] Ru[13] Cu,[14] $Hg(OTf)_2$,[15] Pt,[16] Et_2Zn,[17] Ir.[18]



(YH = nucleophilic group, such as OH, NH)

Scheme 1. Alkyne nucleophile *endo*- or *exo*-cycloisomerization.

Cyclization of alkynols giving *exo*-cyclic enol ethers was first achieved by the use of HgO and $BF_3 \cdot Et_2O$ as the catalysts.[19] Several more catalysts were later found to work well in this reaction: organolanthanide complexes of the form $Ln[N(SiMe_3)_2]_3$, where Ln refers to La, Sm, Y, Lu, Nd;[20] heavier alkaline earth bis(trimethylsilyl)amides;[21] Bu_4NF;[22] and transition metal catalysts, such as $Pd(OAc)_2$,[23] Ag_2CO_3,[24] AuCl,[25] $Cu(OTf)_2$[26] and the Cu(NHC)(Me) complex.[27] Tandem *exo*-cyclization/isomerization reactions of alkynols, which firstly generate *exo*-intermediates and then undergo the isomerization to give the *endo* products, produce *endo*-cyclic enol ethers or furans in the presence of $RuCl_2(PPh_3)$(*p*-cymene)[28] or palladium catalysts, such as $PdCl_2$,[29] $Pd(OAc)_2$[30] and K_2PdI_4.[31] *exo*-Cyclization of aromatic alkynols promoted by stoichiometric NaH has been described,[32] although the same reaction with catalytic amount base as the catalyst has not been reported yet.

As the applications of cyclization of alkynols, recently we applied *exo*-cyclic enol ethers to the reaction with imines, and dihydroisobenzofuran derivatives were obtained in THF and isoquinolin-1(2*H*)-one products were obtained in DMSO.[33] Moreover, the tandem reaction involving Diels–Alder reaction and an

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intermolecular nucleophilic addition reaction for *exo*-cyclic enol ether with benzyne was achieved to afford phenanthro[10.1-*bc*] furan.[34]

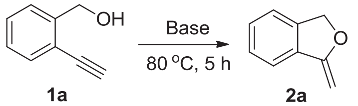
Cyclization of alkynylamines to form *exo*-cyclic products has been developed as the efficient method to construct *N*-heterocyclics,[17,35] and the effective catalysts include phase transfer catalysts,[36] I_2,[37] or Pd.[35d,38] Recently, stoichiometric KH, *t*-BuOK[39] or *t*-BuONa[40] catalyzed cyclization of alkynylamines has been developed to afford indoles or isoindolin-1-ones. To date, however, the same cyclization reaction with catalytic amount base as catalyst has not been reported.

Thus the transition-metal-free cyclization reactions of both alkynylamines and alkynols using commercially available, less expensive catalysts are still highly desirable. Here we report potassium *tert*-butoxide (*t*-BuOK) as the effective catalyst for the *exo*-cycloisomerization of alkynols and alkynylamines. For the alkynols, catalytic reactions exhibit 100% regioselectivity, giving *exo*-cyclic enol ethers in good to excellent yields. The alkynylamines could also do the transformation to give indoles and isoindolin-1-ones in good yields.

2. Results and discussion

First we explored the catalytic activity of *t*-BuOK (10 mol %) in alkynol cyclization using (2-ethynylphenyl)methanol **1a** as the model substrate; we tested the reaction in various solvents at 80 °C (Table 1). Reaction products were analyzed after 5 h by ^{1}H NMR, using $PhSiMe_3$ as the internal standard. The cyclization of **1a** did not proceed in toluene or 1,2-dichloroethane (DCE), and the same reaction in 1,4-dioxane or acetone gave low yields (Table 1, entries 1–4). When the reaction was carried out in THF, **1a** cyclized with 61% yield (entry 5). Yields of cyclic enol ether **2a** were 70–79% when the solvents were acetonitrile, dimethylformamide (DMF), methanol or *N*-methyl-2-pyrrolidone (NMP) (entries 6–9). Surprisingly, when the solvent was dimethyl sulfoxide (DMSO), the reaction produced the cyclized product **2a** exclusively in 94% yield and 100% *exo*-selectivity (entry 10). We suggest that this significant solvent effect is because polar aprotic DMSO stabilizes the anionic reaction intermediate.

Table 1
Cyclization of (2-ethynylphenyl)methanol **1a** under various conditions[a]



1a **2a**

Entry	Solvent	Catalyst	Yield[b] (%)
1	Toluene	*t*-BuOK	0
2	DCE	*t*-BuOK	<5
3	1,4-Dioxane	*t*-BuOK	30
4	Acetone	*t*-BuOK	44
5	THF	*t*-BuOK	61
6	Acetonitrile	*t*-BuOK	70
7	DMF	*t*-BuOK	73
8	Methanol	*t*-BuOK	74
9	NMP	*t*-BuOK	79
10	DMSO	*t*-BuOK	94
11	DMSO	K_2CO_3	64
12	DMSO	KOH	45
13	DMSO	Et_3N	0
14[c]	DMSO	*t*-BuOK	60
15[d]	DMSO	*t*-BuOK	45

[a] Reaction conditions: catalyst (0.1 mmol), **1a** (1.0 mmol), solvent (2 mL), 80 °C, 5 h, unless otherwise noted.
[b] Determined by ^{1}H NMR integration using $PhSiMe_3$ as the internal standard.
[c] *t*-BuOK (0.05 mmol).
[d] At 70 °C.

Changing the cyclization catalyst from *t*-BuOK to weaker bases, such as K_2CO_3 or KOH decreased yields to 64% and 45%, respectively (entries 11 and 12). Similarly, decreasing the loading of *t*-BuOK to 5 mol % or lowering the reaction temperature to 70 °C substantially reduced yields (entries 14 and 15). Note that the organic base triethylamine was ineffective as a catalyst (entry 13).

Next we analyzed the cyclization of various alkynols in DMSO at 80 °C (oil bath temperature), using 10 mol % *t*-BuOK as the catalyst (Table 2). After 5 h, the cyclic enol ether products were obtained with 100% *exo*-selectivity, and their structures were fully consistent with published data for ^{1}H and ^{13}C{^{1}H} NMR and mass spectrometry. ^{1}H NMR analysis of the products, together with single-crystal X-ray diffraction analysis of product **2j** (Fig. 1), indicated that all cyclic enol ether products were pure *Z*-stereoisomers except **2z**. NOESY experiments with **2w** showed that H^1 was close to H^2 and H^3, confirming the *Z*-configuration of the cyclic enol ether products.

Cyclization of both the terminal alkynol **1a** and the internal alkynol bearing a phenyl group on the alkynyl group gave product **2b** in similarly high yield around 94%. Alkynols **2c**,**e**,**f**,**h** and **i**, bearing electron-donating functional groups like NH_2, NHBoc, OMe or Me at *ortho*-, *meta*- or *para*-positions on the aromatic rings gave the corresponding *exo*-cyclic enol ethers in excellent isolated yields of 88–97%. Similar results were observed with alkynols **2d**,**g** and **2j**–**l** bearing electron-withdrawing groups like Cl, F or CF_3 at *ortho*-, *meta*- or *para*-positions on the aromatic rings. These results suggest that neither the nature nor position of electron-donating or electron-withdrawing functional groups on the aromatic ring significantly affect substrate cyclization.

An alkynol with an ester group gave **2m** in slightly lower yield of 83%, demonstrating the tolerance of the ester group under these strongly basic catalytic reaction conditions. The presence of a pyridyl heterocyclic ring on the end of the alkynyl group inhibited cyclization, giving product **2n** in 61% yield. In contrast, the presence of cyclopropyl at the end of the alkynyl group produced the corresponding cyclic enol ether **2o** in 95% yield. The presence of an aliphatic hexyl substituent on the end of the alkynyl group led to complex cyclization results under these reaction conditions.

In the cyclization process, we also investigated the substituent effect of the methylene carbon in the benzyl alcohol. Alkynols with methyl or *n*-butyl substitutions gave products **2p** and **2q** in excellent yields of 97% and 95%, respectively. However, attaching a *tert*-butyl group to the methylene of the benzyl alcohol created so much steric hindrance that cyclization could not proceed. Modifying the aromatic ring of the benzyl alcohol with electron-withdrawing groups, such as F or Cl or with electron-donating groups, such as Me or OMe led to the corresponding products **2r**–**u** in yields of 88–98%. Multisubstituted alkynols were tolerated in the reaction, giving rise to the cyclization products **2v**–**x** in yields of 80–95%. Although these results demonstrate the flexibility of the catalytic system, the highly alkaline conditions may prevent the use of more complicated substrates with base-sensitive functional groups. In addition, cyclization of aliphatic alkynols does not proceed efficiently under these conditions.

To demonstrate the potential usefulness of the alkynol cyclization for generating derivatives of natural products, we focused on an alkynol modified with cholesterol. Cholesterol is an essential structural component of mammalian cell membranes and it serves as a precursor for the biosynthesis of steroid, bile acids and vitamin D.[41] Incubating an alkynol modified with cholesterol **1y** with 10 mol % of *t*-BuOK in THF at 80 °C gave the desired cyclization product **2y** in 94% yield. This reaction did not proceed in DMSO, because the substrate showed poor solubility in that solvent.

To test whether ethynylphenol would react in our cyclization procedure, we incubated 2-((4-methoxyphenyl)ethynyl)phenol with 10 mol % of *t*-BuOK in DMSO at 80 °C. The desired product, 2-(4-methoxyphenyl)benzofuran **2z**, was obtained in 90% yield. This