Potassium Hydroxide-Mediated Cascade Isomerization and Oxy-Michael Addition of 3-(2-Hydroxymethylphenyl)-1-arylprop-2-yn-1-ols Leading to Isobenzofurans

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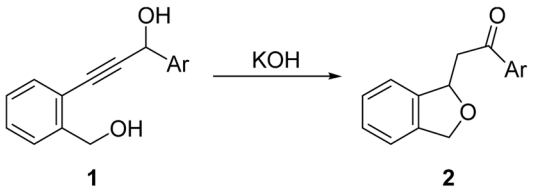
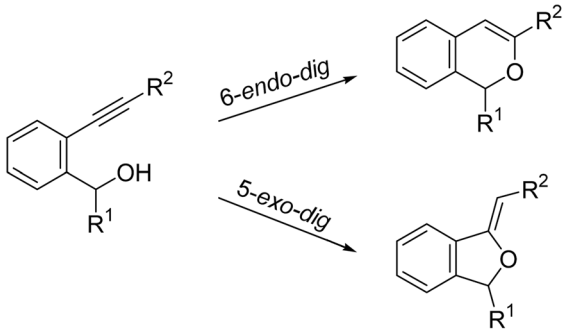
Cycloisomerization for heterocycles has been considered as an attractive method from the viewpoint of atom economy. In connection with this report, 2-alkynylbenzyl alcohols have been used as cycloisomerization precursors for the synthesis of 1,3-dihydroisobenzofurans or 1*H*-isochromenes (Scheme 1). It was reported by Padwa that 2-alkynylbenzyl alcohols having R^2 = aryl group are cycloisomerized to (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans in 5-*exo-dig* mode or 1*H*-isochromenes in 6-*endo-dig* mode under KOH/MeOH according to the kind of substituents on the aromatic ring of R^2.[1] Sakamoto also disclosed that 2-alkynylbenzyl alcohols having R^2 = aryl group are efficiently cycloisomerized in 5-*exo-dig* mode in preference to 6-*endo-dig* mode under tetrabutylammonium fluoride (TBAF), whereas with that having R^2 = butyl the cyclization directed to 6-*endo-dig* mode with poor yield.[2] On the other hand, Gabriele *et al*. have recently reported that 2-alkynylbenzyl alcohols are readily cycloisomerized to 5-*exo-dig* mode or 6-*endo-dig* mode irrespective of R^2 = aryl or alkyl group under palladium-catalyzed neutral conditions, and the cyclization mode is dependent on the substitution pattern of the substrates as well as reaction conditions.[3] Under these circumstances, herein this report describes an unusual consecutive isomerization and cycloisomerization (oxy-Michael addition) of 3-(2-hydroxymethylphenyl)-1-arylprop-2-yn-1-ols to 2-(1,3-dihydroisobenzofuran-1-yl)-1-arylethanones under KOH.[4]

First, the isomerization followed by cycloisomerization (oxy-Michael addition) with 3-(2-hydroxymethylphenyl)-1-phenylprop-2-yn-1-ol (**1a**, **1**: Ar = Ph) was examined under several conditions (Eq. 1). Typically, **1a** was subjected to isomerize and cyclize in the presence of equimolar amount of KOH to afford 2-(1,3-dihydroisobenzofuran-1-yl)-1-phenylethanone (**2a**[5], **2**: Ar = Ph).[6] Among the solvents examined at 80 °C, toluene in terms of both yield and conversion revealed to be the solvent of choice. The reaction was monitored until **1a** had disappeared on TLC, which occurred within 1 h. Dioxane could be alternatively used, but the yield of **2a** was lower than when toluene was used (50% yield for 30 min). Performing the reaction in acetonitrile or DMF resulted in unidentifiable complicated mixture, and the reaction in THF did not proceed effectively and the starting **1a** was recovered almost completely. When the reaction was carried out at 25 °C in dioxane, the isomerization and cycliztion did not occur satisfactorily, **1a** being obtained in only 28% yield.



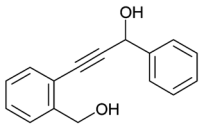
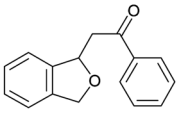
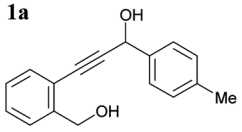
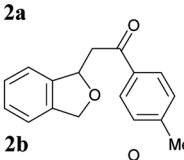
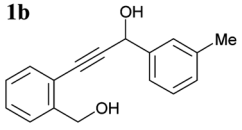
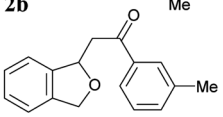
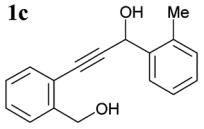
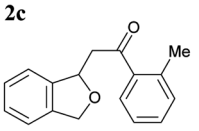
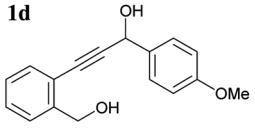
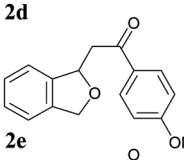
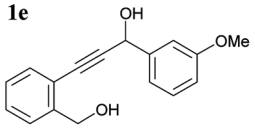
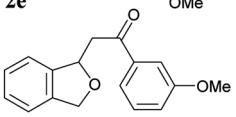
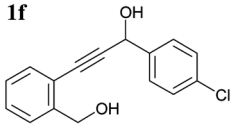
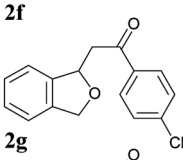
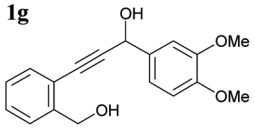
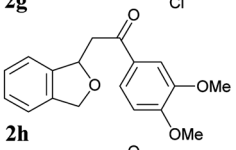
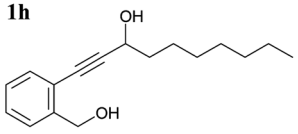
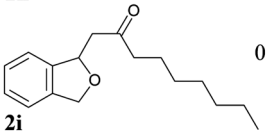
1 **2** (1)

Given the controlled conditions, the isomerization and cycloisomerization of various 3-(2-hydroxymethylphenyl)-1-arylprop-2-yn-1-ols **1**, which are readily available from 2-iodobenzyl alcohol and 1-aryl-2-propyn-1-ols[7] under Sonogashira coupling conditions,[8] were screened in order to synthesize a wide range of 2-(1,3-dihydroisobenzofuran-1-yl)-1-arylethanones **2** (Table 1). With propargyl alcohols (**1b**-**1h**) which have various aryl group attached to propargylic carbon the cycloisomerization products (**2b**-**2h**) were formed in the range of 34-63% yields (entries 1-8). Here again, the startings were disappeared completely within 1 h on TLC analysis. The product yield was not significantly affected by the electronic nature of the substituent on the aromatic ring attached to propargylic carbon of **1b**-**1h**, whereas the position of that had some relevance to the product yield. On the other hand, the reaction with propargyl alcohol **1i** which has an alkyl substituent attached to



Scheme 1

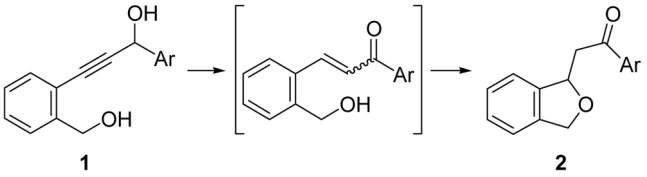
Table 1. Synthesis of 2-(1,3-dihydroisobenzofuran-1-yl)-1-aryl-ethanones **2**[a]

Entry	1	2	Yield (%)
1	 **1a**	 **2a**	61
2	 **1b**	 **2b**	63
3	 **1c**	 **2c**	57
4	 **1d**	 **2d**	34
5[b]	 **1e**	 **2e**	53
6	 **1f**	 **2f**	60
7	 **1g**	 **2g**	42
8	 **1h**	 **2h**	51
9	 **1i**	 **2i**	0

[a]All reactions were carried out with **1** (0.3 mmol) and KOH (0.3 mmol) in toluene (3 mL) at 80 °C for 1 h. [b]In dioxane for 30 min.

propargylic carbon failed to give the cycloisomerization product **2i** (entry 9).

It appears that the reaction proceeds *via* an initial isomerization of **1** to enones and subsequent 5-*exo-trig* cycloisomerization (oxy-Michael addition) (Scheme 2). It is known that several transition metals[9] such as Pd, Ru, Rh and Ir as well as organic bases[10] isomerize propargylic alcohols to enones or enals.[11] It was also reported by several groups that limited halides such as 2-iodopyrimidines, 6-iodouracils, and (chloroarene)$Cr(CO)_3$ are coupled with propargylic alcohols to give coupled enones *via* isomerization of initial coupled propargylic alcohols under Sonogashira coupling conditions.[12]



1 **2**

Scheme 2

In summary, it has been shown that 3-(2-hydroxymethylphenyl)-1-arylprop-2-yn-1-ols undergo cascade isomerization and 5-*exo-trig* cycloisomerization (oxy-Michael addition) to give the corresponding 2-(1,3-dihydroisobenzofuran-1-yl)-1-arylethanones in the presence of KOH. Further study on the synthetic application using the present isomeriztion and oxy-Michael addition is currently under investigation.

Experimental Section

^1H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. The isolation of pure products was carried out via column (silica gel 60, 70-230 mesh, Merck) and thin layer (silica gel 60 GF_{254}, Merck) chromatography. 3-(2-Hydroxymethylphenyl)-1-arylprop-2-yn-1-ols were prepared by the reported method.[4,7,8] Commercially available organic and inorganic compounds were used without further purification except for toluene, which was distilled from calcium hydride.

General procedure for cascade isomerization and Michael addition of 1 leading to 2. A mixture of **1** (0.3 mmol), KOH (0.3 mmol) and toluene (3 mL) was placed in a 5 mL screw-capped vial and allowed to react at 80 °C for 1 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate inorganic salts and concentrated under reduced pressure. The residual mixture was separated by thin-layer chromatography (silica gel, ethyl acetate-hexane mixture) to give **2**. The compounds prepared by the above procedure were characterized spectroscopically as shown below.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-phenylethanone (2a).[5] Solid (hexane-chloroform); mp 80-81 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.34 (dd, J = 5.0 and 16.6 Hz, 1H), 3.54 (dd, J = 7.0 and 16.6 Hz, 1H), 5.07-5.17 (m, 2H), 5.89-5.92 (m, 1H), 7.22-7.31 (m, 4H), 7.43-7.47 (m, 2H), 7.54-7.58 (m, 1H), 7.97-8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.8, 72.8, 80.3, 121.2, 121.7, 127.6, 127.9, 128.5, 128.8, 133.4, 137.3, 139.4, 141.6, 198.0.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-methylphenyl)-ethanone (2b). Solid (hexane-chloroform); mp 70-73 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.40 (s, 3H), 3.31 (dd, J = 5.0 and 16.6 Hz, 1H), 3.51 (dd, J = 7.5 and 16.6 Hz, 1H), 5.06-5.17 (m, 2H), 5.88-5.91 (m, 1H), 7.22-7.31 (m, 6H), 7.89 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1, 45.9, 73.0, 80.6, 121.4, 121.9, 127.8, 128.1, 128.8, 129.7, 135.0,

139.7, 141.9, 144.5, 197.8. Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C 80.59, H 6.39.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(3-methylphenyl)-ethanone (2c). Sticky solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 3.34 (dd, J = 5.1 and 16.7 Hz, 1H), 3.54 (dd, J = 7.3 and 16.7 Hz, 1H), 5.08-5.18 (m, 2H), 5.89-5.92 (m, 1H), 7.23-7.39 (m, 6H), 7.77-7.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 46.1, 73.0, 80.6, 121.4, 121.9, 125.9, 127.9, 128.2, 128.9, 129.2, 134.5, 137.5, 138.8, 139.6, 141.9, 198.5; HRMS Calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1148.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(2-methylphenyl)-ethanone (2d). Viscous oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 3.31 (dd, J = 4.8 and 16.5 Hz, 1H), 3.42 (dd, J = 7.5 and 16.5 Hz, 1H), 5.05-5.13 (m, 2H), 5.84-5.87 (m, 1H), 7.24-7.29 (m, 6H), 7.34-7.38 (m, 1H), 7.66 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.8, 48.8, 73.0, 80.8, 121.4, 121.8, 126.0, 127.8, 128.1, 129.3, 131.8, 132.4, 138.2, 138.9, 139.7, 141.8, 202.1.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-methoxyphenyl)-ethanone (2e). Solid (hexane-chloroform); mp 106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.29 (dd, J = 5.0 and 16.2 Hz, 1H), 3.50 (dd, J = 7.3 and 16.2 Hz, 1H), 3.87 (s, 3H), 5.07-5.17 (m, 2H), 5.87-5.91 (m, 1H), 6.93 (d, J = 9.0 Hz, 2H), 7.23-7.31 (m, 4H), 7.98 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.7, 55.9, 73.0, 80.7, 114.1, 121.4, 121.9, 127.8, 128.1, 130.6, 131.0, 139.6, 142.0, 164.0, 196.7. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.82; H, 6.00.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(3-methoxyphenyl)-ethanone (2f). Sticky solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.34 (dd, J = 5.0 and 16.6 Hz, 1H), 3.53 (dd, J = 7.2 and 16.6 Hz, 1H), 3.85 (s, 3H), 5.07-5.18 (m, 2H), 5.88-5.91 (m, 1H), 7.11 (dd, J = 2.7 and 8.2 Hz, 1H), 7.23-7.30 (m, 4H), 7.36 (t, J = 7.9 Hz, 1H), 7.52-7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.2, 55.9, 73.1, 80.6, 112.7, 120.3, 121.4, 121.5, 121.9, 127.9, 128.2, 130.0, 138.8, 139.6, 141.8, 160.2, 198.2.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(4-chlorophenyl)-ethanone (2g). Solid (hexane-chloroform); mp 85-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.31 (dd, J = 5.0 and 16.6 Hz, 1H), 3.50 (dd, J = 7.5 and 16.6 Hz, 1H), 5.07-5.16 (m, 2H), 5.86-5.89 (m, 1H), 7.23-7.32 (m, 4H), 7.43 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.0, 73.1, 80.5, 121.5, 121.8, 127.9, 128.3, 129.3, 130.1, 135.8, 139.6, 140.1, 141.6, 197.1.

2-(1,3-Dihydroisobenzofuran-1-yl)-1-(3,4-dimethoxyphenyl)ethanone (2h). Solid (hexane-chloroform); mp 97-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.30 (dd, J = 5.0 and 16.6 Hz, 1H), 3.52 (dd, J = 7.3 and 16.6 Hz, 1H), 3.93 (s, 3H), 3.94 (s, 3H), 5.07-5.17 (m, 2H), 5.88-5.91 (m, 1H), 6.88 (d, J = 8.0 Hz, 1H), 7.23-7.31 (m, 4H), 7.59-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 45.5, 56.4, 56.5, 73.0, 80.8, 110.4, 110.6, 121.4, 121.9, 123.5, 127.8, 128.1, 130.8, 139.6, 141.9, 149.4, 153.8, 196.8. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.28; 6.26.

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