LETTERS

Direct Preparation of 3-lodochromenes from 3-Aryl- and 3-Alkyl-2propyn-1-ols with Diaryliodonium Salts and NIS

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Supporting Information

ABSTRACT: On the basis of a study of the *O*-phenylation of 3-phenyl-2-propyn-1-ol with diphenyliodonium triflate and *t*-BuONa, a variety of 4-aryl-3-iodo-2*H*benzopyrans were prepared in good to moderate yields in one pot from the reaction of 3-aryl-2-propyn-1-ols with diaryliodonium triflates and *t*-BuONa, followed by the treatment with *N*-iodosuccinimide and BF₃·OEt₂, under transition-metal-free and mild conditions. The formed 4-phenyl-3-iodo-2*H*-



benzopyran was converted into 4-phenyl-2H-benzopyran derivatives through C-C bond formations at the 3-position by Pdcatalyzed coupling reactions and into coumarin with oxidants.

hromene (2H-1-benzopyran) is an important building unit because it is a precursor or an intermediate of natural products, particularly for coumarins, and medicinals.¹ Chromene derivatives bearing anti-HIV,^{2a} antitumor,^{2b} and antibacterial activities^{2c,d} are known. The coumarin unit is a key structure of natural products and biologically active molecules.³ Extensive studies of the preparation of 2H-benzopyrans have been carried out.⁴ Typically, 2H-benzopyrans are prepared by the cyclization of allyl o-vinylaryl ethers with Rh catalyst through an intramolecular ene-metathesis reaction (RCM),^{4c,d} the cyclization of α -(o-hydroxyaryl)allyl alcohols with Au catalyst via *endo*-cyclization,^{4e} and the cyclization of aryl propargyl ethers with Au, Ag, or Pt catalyst.^{4f-i} An InI_3 catalyzed cyclization of aryl propargyl ethers^{4j} and a AgOTfcatalyzed cycloisomerization of cyclopropyl(o-hydroxyphenyl)carbinols^{4k} into 2H-benzopyrans were also reported. As transition-metal-free conditions, an IPy2BF4 and HBF4 system in dichloromethane⁵ and an I₂, ICl, or PhSeBr system in nitromethane⁶ were used for the electrophilic iodocyclization of aryl propargyl ethers to form 3-iodo-2H-benzopyrans.

It is well-known that diaryliodonium salts are efficient reagents for the *O*-arylation of phenols, alcohols, carboxylic acids, and oximes under transition-metal-free conditions.⁷ We previously reported the *O*-arylation of various phenols using diaryliodonium salts.⁷¹ Here, as part of our study of diaryliodonium salts for organic synthesis, we report a one-pot preparation of 3-iodo-2*H*-benzopyrans through the reaction of 3-aryl-2-propyn-1-ols and 3-alkyl-2-propyn-1-ols with diaryliodoniums triflates and *t*-BuONa followed by the reaction with *N*-iodosuccinimide (NIS) and BF₃·OEt₂ under transition-metal-free conditions.

First, the O-arylation of 3-phenyl-2-propyn-1-ol 1a with diphenyliodonium triflate A in the presence of bases, such as NaH, *t*-BuONa, *t*-BuOK. *t*-BuOLi, K_2CO_3 , and Cs_2CO_3 in DMF, THF, benzene, toluene, and acetonitrile, was carried out as shown in Table 1. Initial screening experiments revealed that

Table 1. O-Phenylation of 3-Phenyl-2-propyn-1-ol

Ph₂l ⁺ TfO⁻(A , 1.1 equiv)								
	Ph 🗕 🔨	base (1.1 equ	iiv) 🛌 Ph					
	0	H solvent (3.0 mL), te	solvent (3.0 mL), temp, time		OPh			
	1a			2Aa				
entry	base	solvent	temp (°C)	time (h)	yield (%)			
1	NaH	DMF	0 to 80	7	40			
2	t-BuONa	DMF	0 to 60	5	70			
3	t-BuONa	THF	0 to reflux	5	46			
4	t-BuONa	benzene	0 to 60	25	79			
5	t-BuONa	toluene	0 to 60	23	72			
6	t-BuOK	benzene	0 to 60	2	78			
7	t-BuOLi	benzene	0 to 60	7	39			
8 ^a	K ₂ CO ₃	toluene	0 to 60	15	39			
9	K ₂ CO ₃	CH ₃ CN	0 to 60	5	3			
10	Cs ₂ CO ₃	benene	0 to 60	5	79			
11	t-BuONa	benzene/DCE (1:1)	0 to 60	3	83			
12 ^b	t-BuONa	benzene/DCE (1:1)	0 to 60	3	89			
13 ^c	t-BuONa	benzene/DCE (1:1)	0 to 60	3	87			
^{<i>a</i>} 18-Crown-6 (10 mol %) was added. ^{<i>b</i>} MgSO ₄ (0.2 equiv) was added c MgSO ₄ (0.5 equiv) was added.								

use of *t*-BuONa as the base in DMF, THF, benzene, or toluene gave phenyl 3-phenyl-2-propynyl ether **2Aa** in moderate to good yields (Table 1, entries 1–10). Optimization of base in benzene was performed, and it was found that *t*-BuONa and Cs_2CO_3 in benzene were the best choices (Table 1, entries 4 and 10). Optimization of solvent revealed that the mixture of benzene and 1,2-dichloroethane (benzene/DCE = 1:1) was the most suitable (Table 1, entries 11–13), and the addition of MgSO₄ enhanced the reaction (Table 1, entries 12 and 13). *t*-BuONa is less expensive than deliquescent Cs_2CO_3 . Finally, *t*-

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BuONa as a base and $MgSO_4$ were chosen for the present reaction. Next, the optimum conditions for the iodocyclization of phenyl 3-phenyl-2-propynyl ether **2Aa** with NIS were studied, as shown in Table 2. When phenyl 3-phenyl-2-

Table 2. Iodocyclization of Phenyl 3-Phenyl-2-propynylEther to 3-Iodo-4-phenyl-2H-benzopyran 3Aa

Ph		NIS (additive	1.1 equiv) e (1.1 equiv)), ,			
	2Aa	solvent (5.0	mL), temp, tim	e 3Aa ^F	'n			
entry	additive	solvent	temp (°C)	time (h)	yield (%)			
1		CH ₃ CN	0 to rt	7	0			
$2^{a,b}$	I_2	CH ₃ CN	0 to rt	3	55			
$3^{b,c}$	I_2	CH ₃ CN	0 to rt	3	35			
4 ^{<i>d</i>}	I_2	CH ₃ CN	rt	16	66			
5 ^{<i>a,b</i>}	I_2	DCM	0 to rt	3	63			
6	I_2	DCM	0 to rt	3	83			
7	$BF_3 \cdot OEt_2$	DCM	0	0.5	91			
8 ^{<i>a,e</i>}	$BF_3 \cdot OEt_2$	DCM	0	0.5	72			
aNIE (20 again) was used by dditions (10 again) was used CDILI (10								

^aNIS (2.0 equiv) was used. ^bAdditive (1.0 equiv) was used. ^cDIH (1.0 equiv) was used instead of NIS. ^dI₂ (3.0 equiv) and NaHCO₃ (3.0 equiv) were used, without NIS. ^eAdditive (2.0 equiv) was used.

propynyl ether 2Aa was treated with NIS only in CH₃CN, 3iodo-4-phenyl-2H-benzopyran 3Aa was not obtained at all (Table 2, entry 1). The addition of I_2 (1.0 equiv) induced iodocyclization to provide 3-iodo-4-phenyl-2H-benzopyran 3Aa in moderate yield (Table 2, entry 2). Use of 1,3-diiodo-5,5dimethylhydantoin (DIH) instead of NIS did not enhance the reaction (Table 2, entry 3). Employing I_2 (3.0 equiv) and NaHCO₃ (3.0 equiv) in the absence of NIS gave 3-iodo-4phenyl-2H-benzopyran 3Aa in 66% yield (Table 2, entry 4). Dichloromethane (DCM) was a better solvent than CH₃CN as a solvent (Table 2, entries 2 and 5), and treatment of phenyl 3phenyl-2-propynyl ether 2Aa with NIS (1.1 equiv) and I_2 (1.1 equiv) in CH₂Cl₂ at 0 °C gave 3-iodo-4-phenyl-2H-benzopyran **3Aa** in 83% yield (Table 2, entry 6). The addition of $BF_3 \cdot OEt_2$ instead of I₂ markedly improved the reactivity: treatment of phenyl 3-phenyl-2-propynyl ether 2Aa with NIS (1.1 equiv) and BF₃·OEt₂ (1.1 equiv) in DCM at 0 °C for 30 min gave 3iodo-4-phenyl-2H-benzopyran 3Aa in 91% yield (Table 2, entry 7). On the other hand, the addition of excess NIS (2.0 equiv) and $BF_3 \cdot OEt_2$ (2.0 equiv) reduced the yield of compound 3Aa (Table 2, entry 8). On the basis of the results in Tables 1 and 2, a one-pot transformation of 3-phenyl-2-propyn-1-ol 1a into 3iodo-4-phenyl-2H-benzopyran 3Aa was carried out. 3-Phenyl-2propyn-1-ol 1a was treated with diphenyliodonium triflate A in the presence of t-BuONa and MgSO4 in a mixture of benzene and DCE (1:1) at 60 °C for 3 h, and this was followed by the reaction with NIS (1.1 equiv) and BF₃·OEt₂ (1.1 equiv) under various reaction conditions to give 3-iodo-4-phenyl-2Hbenzopyran 3Aa. It was found that evaporation prior to the second reaction step was not necessary for this reaction. Consequently, the addition of DCM (3 mL) prior to the second reaction step was the most effective. The use of 0.5 equiv of BF₃·OEt₂ afforded low reactivity, and BCl₃, BBr₃, and $B(C_6F_5)_3$ also showed low reactivity, particularly BBr₃ (see the Supporting Information). Thus, it was clarified that the treatment of 3-phenyl-2-propyn-1-ol 1a with t-BuONa (1.1 equiv) and diphenyliodonium triflate A (1.1 equiv) in the presence of MgSO₄ in a mixture of benzene and DCE (1:1) at

60 °C for 3 h, followed by the reaction with NIS (1.1 equiv) and BF₃·OEt₂ (1.1 equiv) at 0 °C for 1 h, together with the addition of DCM (3.0 mL) was the best to give 3-iodo-4-phenyl-2H-benzopyran **3Aa** in 80% yield, as shown in Scheme 1. A gram-scale preparation of 3-iodo-4-phenyl-2H-benzopyran

Scheme 1. One-Pot Transformation of 3-Aryl-2-propyn-1-ols and 3-Alkyl-2-propyn-1-ols into 3-Iodo-2*H*-Benzopyrans 2 with Diphenyliodonium Triflate A



^aStarting material (8.0 mmol) was used. ^bThe second reaction step was carried out for 2 h. ^cThe second reaction step was conducted at -20 °C for 30 min. ^dThe second reaction step was conducted at -10 °C for 20 h. ^eThe second reaction step was carried out for 30 min.

3Aa from 3-phenyl-2-propyn-1-ol **1a** (8 mmol) was also successfully carried out in 82% yield, as shown in Scheme 1. Using the optimum reaction conditions, various 3-aryl-2-propyn-1-ols **1b**-**k**, bearing *p*-fluorophenyl, *p*-chlorophenyl, *p*-methylphenyl, *m*-methylphenyl, *o*-methylphenyl, *p*-biphenyl, *p*-benzyloxyphenyl, 1-naphthyl, and 2-naphthyl groups at the 3-position, were treated with diphenyliodonium triflate **A** in the presence of *t*-BuONa and MgSO₄ in a mixture of benzene and DCE (1:1) at 60 °C for 3 h, followed by the reaction with NIS and BF₃·OEt₂ at 0 °C for 1 h, to give

the corresponding 3-iodo-4-aryl-2H-benzopyrans 3Ab-Ak in good yields, as shown in Scheme 1. Thus, 3-aryl-2-propyn-1-ols 1 bearing an electron-withdrawing group or an electrondonating group on the aromatic ring gave the corresponding 3iodo-4-aryl-2H-benzopyrans 3 in good yields. The same treatment of 3-aryl-2-propyn-1-ols 11-o bearing heteroaromatic groups, such as 5-methyl-2-furyl, 2-benzofuryl, 2-benzothienyl, and 1-(benzenesulfonyl)-3-indolyl groups at the 3-position of the 3-aryl-2-propyn-1-ols, also gave the corresponding 3-iodo-4aryl-2H-benzopyrans 3Al-Ao in good to moderate yields, respectively. In addition, the same treatment of 3-styryl-2propyn-1-ol 1p and 3-alkyl-2-propyn-1-ols, such as 2-hexyn-1-ol 1q and 2-decyn-1-ol 1r, also gave 4-styryl- and 4-alkyl-3-iodo-2H-benzopyrans 3Ap-Ar in good to moderate yields, respectively. In total, the yields of compounds 3 with 3-alkyl-2-propyn-1-ols were lower than those with 3-aryl-2-propyn-1ols. We propose two reasons for this: one is that the Ophenylation of 3-alkyl-2-propyn-1-ols 1 with diphenyliodonium triflate A and t-BuONa does not proceed as smoothly as that of 3-aryl-2-propyn-1-ols 1, and the other is that 4-alkyl-3-iodo-2Hbenzopyrans 3Aq and 3Ar are not as stable as 4-aryl-3-iodo-2Hbenzopyrans 3Aa-Ao at room temperature. The same treatment of 4-phenyl-3-butyn-2-ol 1s, a secondary propargyl alcohol, gave 3-iodo-2-methyl-4-phenyl-2H-benzopyran 3As in moderate vield.

Then, the substituent effect on the O-arylation of 3-phenyl-2propyn-1-ol **1a** with diaryliodonium salts, such as di(*p*methylphenyl)iodonium triflate **B**, di(*p*-chlorophenyl)iodonium triflate **C**, di(*p*-bromophenyl)iodonium triflate **D**, and di(*p*-tert-butylphenyl)iodonium triflate **E**, in the presence of *t*-BuONa and MgSO₄ in a mixture of benzene and DCE (1:1) at 60 °C for 3 h followed by the reaction with NIS and BF₃·OEt₂ at 0 °C was studied. 6-Methyl-3-iodo-4-phenyl-2*H*benzopyran **3Ba**, 6-chloro-3-iodo-4-phenyl-2*H*-benzopyran **3Ca**, and 6-bromo-3-iodo-4-phenyl-2*H*-benzopyran **3Da** were produced in good yields, as shown in Scheme 2, whereas the yield of 6-tert-butyl-3-iodo-4-phenyl-2*H*-benzopyran **3Ea** was moderate.

The structure of 6-bromo-3-iodo-4-phenyl-2*H*-benzopyran **3Da** was determined by X-ray crystallographic analysis (see the Supporting Information).





^aThe second reaction step was carried out for 2 h. ^bNIS (1.3 equiv) and BF₃·OEt₂ (1.3 equiv) were used. ^cNIS (0.3 equiv) and BF₃·OEt₂ (0.3 equiv) were added after the second reaction step.

The plausible reaction mechanism for the present iodocyclization is shown in Scheme 3. Thus, BF₃ promotes NISiodocyclization of aryl 3-aryl(alkyl)-2-propynyl ether 2 to 3iodo-4-aryl(alkyl)-2H-benzopyran 3 through the intermediates I and II.

Scheme 3. Plausible Reaction Mechanism for Iodocyclization



Finally, the functional group transformation of 3-iodo-4phenyl-2*H*-benzopyran **3Aa** was carried out, as shown in Scheme 4, as chromenes and coumarins are important units for pharmaceuticals and biologically active compounds.³





Oxidation of 3-iodo-4-phenyl-2H-benzopyran 3Aa into 3iodo-4-phenyl-2H-1-benzopyran-2-one 4Aa was carried out in 56% yield by the reaction with PCC in DCM. Reduction of 3iodo-4-phenyl-2H-benzopyran 3Aa into 4-phenyl-2H-benzopyran 5Aa was carried out in 89% yield by treatment with Zn in ethanol. Oxidation of 4-phenyl-2H-benzopyran 5Aa by DDQ gave γ -phenylcoumarin 6Aa in 72% yield. Then, the Sonogashira coupling reaction of 3-iodo-4-phenyl-2H-benzopyran 3Aa with phenylacetylene and the Suzuki-Miyaura coupling reaction of 3-iodo-4-phenyl-2H-benzopyran 3Aa with phenylboronic acid and PdCl₂(PPh₃)₂ provided the corresponding coupling products 7Aa and 8Aa in 73% and 99% yields, respectively. Moreover, treatment of 3-iodo-4-phenyl-2H-benzopyran 3Aa with *i*-PrMgCl at -78 °C followed by the reaction with ClCO₂Me provided 3-(methoxycarbonyl)-4phenyl-2H-benzopyran 9Aa in 65% yield.

In conclusion, 3-aryl-2-propyn-1-ols and 3-alkyl-2-propyn-1ols were treated with diaryliodonium triflates in the presence of *t*-BuONa followed by a reaction with NIS and $BF_3 \cdot OEt_2$ to give 3-iodo-4-aryl(alkyl)-2H-benzopyrans in good to moderate yields in one pot under mild and transition-metal-free conditions, and the products can be functionalized by oxidation or C–C bond-coupling reactions. The present one-pot method would be useful for the preparation of various 3-iodo-4-aryl-2H-benzopyrans and their derivatives.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b03651.

Experimental details, characterization data by IR, H NMR, and C NMR of all products 3 (PDF) X-ray analysis of **3Da** (CIF)

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Notes

The authors declare no competing financial interest.

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