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Novel One-Pot Method for Chemoselective Bromination and Sequential Sonogashira Coupling

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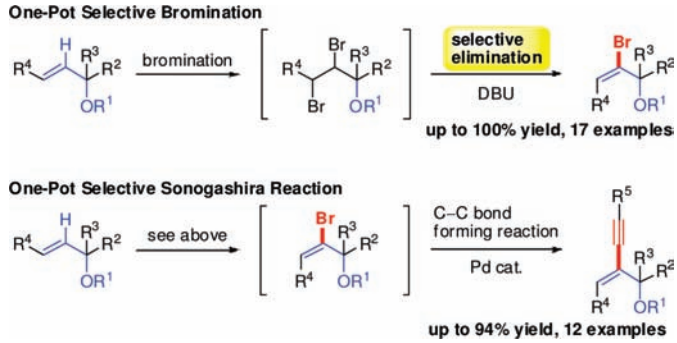
ABSTRACT



An efficient one-pot method for bromination−elimination of allyl alcohol derivatives and sequential Sonogashira coupling has been developed. A highlight of the method is chemoselective DBU-promoted elimination of vicinal dibromoalkanes having an adjacent *O*-functional group.

Carbon−carbon bond-forming reactions of organometallic reagents, such as the Sonogashira[1] and Suzuki−Miyaura[2] coupling processes, play key roles in the total synthesis of natural products[1d−g] and as a result in investigations of biologically active compounds. The applicability of these C−C bond-forming reactions to the synthesis of complex molecules is heightened by the fact that they require simple and mild reaction conditions and that they tolerate an array of potentially labile functionalities. Alkenyl halides are useful building blocks in a wide range of transition-metal-catalyzed C−C coupling reactions as well as in the preparation of vinyllithiums[3] and vinyl Grignard reagents, substrates of radical reactions,[4] and precursors of α-haloketones[5] and heterocycles.[6]

Pawluć et al. recently reported a one-pot synthesis of *trans*-1-bromo-1-alkenes from styrenes by sequential ruthenium-catalyzed silylative coupling followed by an *N*-halosuccinimide-mediated halodesilylation reaction.[7] Moreover, Rault

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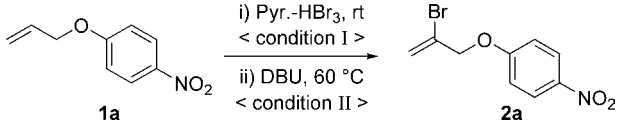
et al. reported a one-pot microwave-promoted synthesis of *cis*-1-bromo-1-alkenes from *anti*-2,3-dibromo-3-arylalkanoic acid followed by Suzuki−Miyaura coupling to afford *cis*-stilbenes.[8] Kuang et al. also reported a one-pot synthesis of *cis*-1-bromo-1-alkenes from *anti*-2,3-dibromo-3-arylalkanoic acid followed by Sonogashira coupling to afford the corresponding enynes under microwave irradiation.[9] Those one-pot syntheses are highly efficient.

However, very little is known about the systematic synthesis of 2-bromo-1-alkenes yet,[10a−d] although a few sporadic examples exist of such syntheses.[11] Herein, we disclose a concise one-pot method for highly chemoselective monobromination of allyl alcohol derivatives and sequential Sonogashira coupling.

We anticipated that bromine addition to allyl alcohol derivatives, followed by Ohgiya−Nishiyama's method for selective elimination,[10] could be suitable for one-pot C2-selective bromination of allyl alcohol derivatives. Therefore, we started our investigations with 1-(allyloxy)-4-nitrobenzene **1a** as a substrate, pyridinium bromide perbromide ($Pyr{\cdot}HBr_3$) as a manageable brominating agent and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as a mild base (Table 1). In a general procedure, **1a** and pyridinium bromide perbromide (1.1 equiv) were stirred at room temperature for 12−14 h. DBU was added to the reaction system at 0 °C, and the system was heated to 60 °C. The reaction was quenched with saturated aqueous NH_4Cl or 1 M aqueous HCl, and the reaction mixture was extracted with dichloromethane or chloroform, concentrated in vacuo, and purified by silica gel column chromatography. When 3.1 equiv of DBU was used, the reaction gave the desired 2-bromo-1-alkene **2a** together with tiny amounts of regioisomers in a 99% overall yield (entry 2). In contrast, when 2.2 equiv of DBU was used, the reaction gave not only a small amount of **2a** but also the intermediate dibromoalkane as a major product (entry 1). The solvent effect of acetonitrile on yield is comparable to that of 1,2-dichloroethane, although the other solvents slow down the rate of initial bromine addition (entries 2−6). Significantly, when 1.1 equiv of potassium carbonate, rather than pyridine, was added as a HBr scavenger before addition of DBU, the requisite amounts of DBU were successfully reduced (entries 7−9). Thus, we found that two optimal conditions (entries 2 and 9) allowed efficient and versatile one-pot synthesis of 2-bromo allyl alcohol derivatives **2** from allyl alcohol derivatives **1** (Scheme 1).

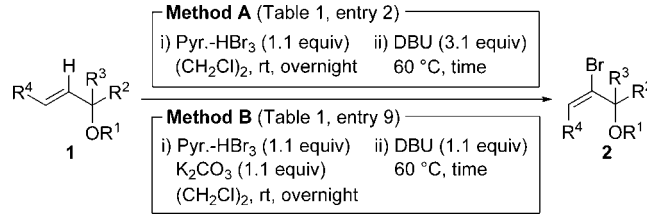
Table 1. Optimization of One-Pot Selective Bromination



	condition I[a]		condition II		
entry	additive (equiv)	solvent	equiv of DBU	time (h)	yield (%); ratio[b] (2-bromo/1-bromo)
1		$(CH_2Cl)_2$	2.2	48.0	6[c]; 45/1
2		**$(CH_2Cl)_2$**	**3.1**	**0.2**	**99; 46/1**
3		DMF	3.1	0.2	68[d]; 48/1
4		THF	3.1	1.5	71[e]; 48/1
5		CH_3CN	3.1	0.3	92; 45/1
6		toluene	3.1	0.4	64[f]; 30/1
7	pyridine (1.0)	$(CH_2Cl)_2$	1.1	7.5	0[g]
8	pyridine (1.0)	$(CH_2Cl)_2$	2.2	3.0	88[h]; 37/1
9	**K_2CO_3 (1.0)**	**$(CH_2Cl)_2$**	**1.1**	**1.0**	**91; 39/1**

[a] The typical reaction times for bromination were between 12 and 14 h. [b] Ratio of 2-bromoalkene and 1-bromoalkene was determined by ^1H NMR. [c] Dibromoalkane was obtained (58%). [d] **1a** was recovered (22%). [e] **1a** was recovered (26%). [f] **1a** was recovered (29%). [g] Dibromoalkane was obtained (86%). [h] **1a** was recovered (6%).

Scheme 1. One-Pot C2-Selective Bromination of Allyl Alcohol Derivatives **1**



To confirm the generality of the one-pot chemoselective bromination reaction, we examined a variety of allyl alcohol derivatives **1** using optimized Method A and/or B (Table 2). First, the allyl alcohols (2-propen-1-ol), which are protected by substituted phenyl (**2b**−**2f**), benzyl (**2g**, **2h**), benzoyl (**2i**−**2k**), and silyl (**2l**) groups, were investigated (entries 1−15). As explained by Nishiyama et al.,[10] the yields and regioselectivity of the DBU-promoted elimination reaction seem to be controlled by the inductive electron-withdrawing effects of *O*-functional groups at the neighboring position. However, compound **2g**, which has an electron-donating PMB group, was obtained in high yield and selectivity (entry 7). Surprisingly, compound **2l**, with an electron-donating bulky triisopropylsilyl group, was also obtained in moderate yield and satisfactory selectivity (entries 14 and 15). In general, Method B requires a longer time for the elimination reaction than does Method A.

Next, we examined more complicated substrates. For secondary alcohol derivatives **2m**, **2p**, and **2q**, yields and selectivities were excellent (entries 16, 17, and 21−24), although tertiary alcohol derivative **2n** was produced in only

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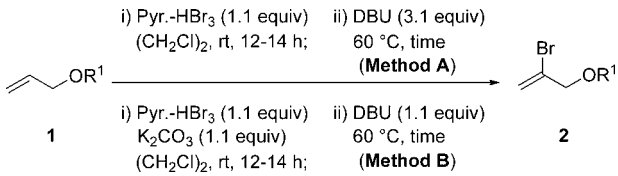
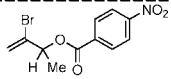
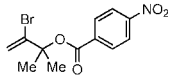
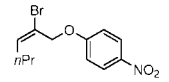
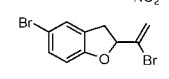
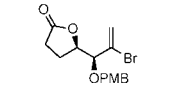
Table 2. Synthesis of 2-Bromo Allyl Alcohol Derivatives **2** Using One-Pot Chemoselective Bromination



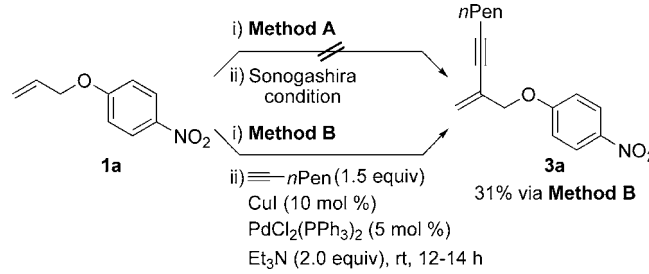
entry	products R^1		Method	time (h)	yield (%)	ratio[a]
1	*o*NO$_2$C$_6$H$_4$	(**2b**)	**A**	0.2	91	> 99 / 1
2	*p*MeOC$_6$H$_4$	(**2c**)	**A**	0.5	92	31 / 1
3	*p*ClC$_6$H$_4$	(**2d**)	**A**	0.5	94	29 / 1
4	*p*BrC$_6$H$_4$	(**2e**)	**A**	0.8	95	25 / 1
5	C$_6$H$_5$	(**2f**)	**A**	0.5	92	18 / 1
6			**B**	0.8	89	17 / 1
7	*p*MeOC$_6$H$_4$CH$_2$	(**2g**)	**B**	6.5	90	15 / 1
8	*p*ClC$_6$H$_4$CH$_2$	(**2h**)	**A**	0.3	96	16 / 1
9			**B**	2.0	93	13 / 1
10	*p*NO$_2$C$_6$H$_4$C(O)	(**2i**)	**A**	0.2	87	31 / 1
11			**B**	6.0	78[b]	28 / 1
12	*p*MeOC$_6$H$_4$C(O)	(**2j**)	**A**	0.2	92	20 / 1
13	*p*ClC$_6$H$_4$C(O)	(**2k**)	**B**	1.8	90	20 / 1
14	TIPS	(**2l**)	**A**	1.0	69[c]	10 / 1
15			**B**	7.0	60[d]	12 / 1
16		(**2m**)	**A**	0.1	91	49 / 1
17			**B**	6.0	92	40 / 1
18		(**2n**)	**A**	1.0	34	8 / 1
19		(**2o**)	**A**	1.0	100	> 99 / 1
20			**B**	7.0	95	> 99 / 1
21		(**2p**)	**A**	1.5	90	> 99 / 1
22			**B**	1.0	93	> 99 / 1
23		(**2q**)	**A**	0.3	94	57 / 1
24			**B**	4.5	94	21 / 1

[a] Ratio of 2-bromoalkene and 1-bromoalkene was determined by ^{1}H NMR. [b] Dibromoalkane was obtained (9%). [c] Dibromoalkane was obtained (27%). [d] Dibromoalkane was obtained (34%).

34% yield (entry 18). Interestingly, reaction of the internal double bond takes place in a highly stereoselective manner involving *trans* elimination to afford **2o** (entries 19 and 20). Thus, as mentioned above, we developed an efficient and concise one-pot method for chemoselective bromination of allyl alcohol derivatives. Our method requires no extra-dry conditions, expensive reagents, or complex manipulations. Moreover, the one-pot bromine addition and subsequent DBU-promoted elimination reactions proceed smoothly even in the presence of sensitive functional groups.

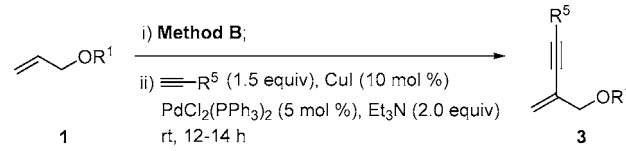
On the basis of these encouraging results, we focused next on developing a one-pot method for the sequential Sonogashira coupling reaction. In our first attempts, the applicability of the three-step reaction sequence (bromine addition, elimination, Sonogashira coupling) was verified using **1a** as a starting material and 1-heptyne as a coupling partner by Methods A and B (Scheme 2).

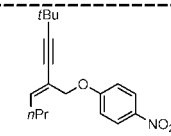
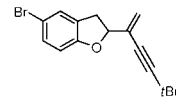
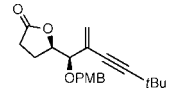
Scheme 2. One-Pot C2-Selective Sonogashira Coupling Reaction of Allyl Alcohol Derivatives **1a**



Synthesis of the desired enyne system **3a** was accomplished in 31% yield by Method B and the following typical Sonogashira conditions.[1] In the general procedure,

Table 3. Synthesis of Enyne Alcohol Derivatives **3** Using One-Pot Chemoselective Sonogashira Coupling Reaction



entry	products R^1	R^5		yield (%)
1	*p*NO$_2$C$_6$H$_4$	*t*Bu	(**3b**)	29
2	*p*MeOC$_6$H$_4$	*n*Pen	(**3c**)	84
3	*p*MeOC$_6$H$_4$	*t*Bu	(**3d**)	91
4	*p*MeOC$_6$H$_4$	C$_6$H$_5$	(**3e**)	81
5	*p*MeOC$_6$H$_4$	*p*MeOC$_6$H$_4$	(**3f**)	70
6	C$_6$H$_5$	*n*Pen	(**3g**)	93
7	C$_6$H$_5$	*t*Bu	(**3h**)	94
8	*p*MeOC$_6$H$_4$CH$_2$	*n*Pen	(**3i**)	70[a]
9			(**3j**)	28[a,b]
10[c]			(**3k**)	77
11			(**3l**)	82

[a] Determined by ^{1}H NMR using 1,4-bis(trimethylsilyl)-benzene as internal standard. [b] The intermediate **2o** was obtained (46%). [c] 3.0 equiv of 3,3-dimethyl-1-butynes was used.

CuI (10 mol %), $PdCl_2(PPh_3)_2$ catalyst (5 mol %), Et_3N (2.0 equiv), and 1-heptyne (1.5 equiv) were added to the reaction mixture at 0 °C after the process of Method B and stirred at room temperature for 12−14 h. Reaction was quenched with saturated aqueous NH_4Cl or 1 M aqueous HCl, and the reaction mixture was extracted with dichloromethane or chloroform, concentrated in vacuo, and purified by silica gel column chromatography with hexane/ethyl acetate to afford **3a** as a sole product. In contrast, consecutive Sonogashira coupling did not proceed at all after the process of Method A.

Satisfied with these results, we carried out three-step sequential reactions of a variety of allyl alcohol derivatives **1** (Table 3). The allyl alcohols having aryloxy groups were easily converted to the enyne adducts **3** by chemoselective bromination and sequential Sonogashira coupling (entries 2−7), except for those having the 4-nitrophenyl group (entries 1 and 9). The syntheses of **3i** and **3l**, with a *p*-methoxybenzyloxy group and/or a lactone moiety, also proceeded in good yields (entries 8 and 11). Intriguingly, the intermediate **2p** of the three-step sequential reaction was converted to **3k** in 77% yield, although 3.0 equiv of 3,3-dimethyl-1-butynes was used as a alkyne unit (entry 10). It is noteworthy that the expected diyne byproduct was detected in only trace amounts, and the plausible aromatic alkyne was not detected at all.

In conclusion, a novel one-pot method for chemoselective bromination of allyl alcohol derivatives has been developed. This synthetic approach should be applicable to the total synthesis of natural products and for use in modern drug-discovery research. Moreover, an efficient one-pot method for Sonogashira coupling was also achieved. A highlight of this study is that the third coupling reaction catalyzed by the transition-metal-based system in this sequence proceeds successfully. We believe that this is a good first step toward achieving diverse chemoselective C−C bond-forming reactions. Further potential applications of this straightforward method are under investigation.

Acknowledgment. We thank Dr. Tadaaki Ohgiya (Manager, Organic Chemistry Department, Organic Chemistry Group I, Tokyo New Drug Research Laboratories, Pharmaceutical Division, Kowa Company, Ltd.) for chemical discussions. This work was partly supported by the Sasakawa Scientific Research Grant from The Japan Science Society.

Supporting Information Available: Spectroscopic data and experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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