

# ONE-STEP TRANSFORMATION OF 2- OR 3-(1-HYDROXYALKYL)-2, 3-DIHYDROBENZOFURANS TO THE ACYLBENZOFURANS WITH *N*-BROMOSUCCINIMIDE

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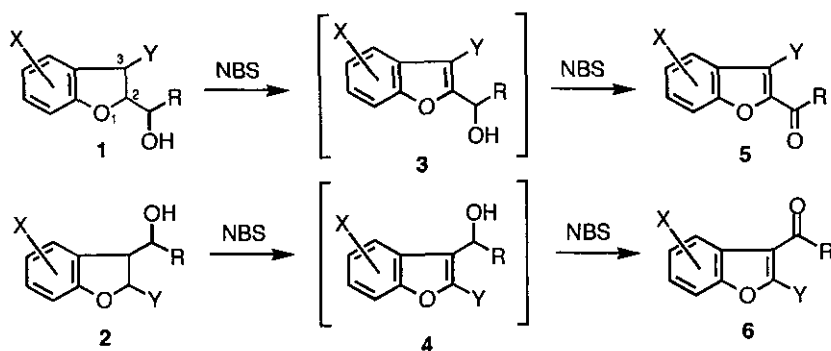
**Abstract**—The one-step transformation of 2- or 3-(1-hydroxyalkyl)-2, 3-dihydrobenzofurans (**1** or **2**) to the 2- or 3-acylbenzofurans (**5** or **6**) with *N*-bromosuccinimide was performed with good yields. The reaction is characterized to take place *via* the continuous bromination–dehydrobromination process. Yields are dependent on the solvent and the kind of additive compounds as a scavenger of the hydrogen bromide by-produced during the reaction.

The oxidation of benzyl alcohols to benzaldehydes using *N*-haloimide is well-known.<sup>1</sup> On the other hand, this agent reacts with olefins to add a halogen to the double bond in an ionic manner and also acts as an agent for halogenation at the allylic or benzylic position in a radical manner. In particular, *N*-bromosuccinimide (NBS) which is used as a specific agent for allylic monobromination has been successfully used to introduce double bonds. The method involves the bromination–dehydrobromination process. In many cases, the intermediate bromide is isolatable and the dehydrobromination proceeds with treatment by a base.<sup>2</sup> However, if aromatization is the driving force of the dehydrobromination, the intermediate would be labile under the reaction conditions and spontaneously lost hydrogen bromide to form an elimination product.<sup>3</sup>

We now wish to report the one-step transformation of the 2- or 3-(1-hydroxyalkyl)-2, 3-dihydrobenzofurans (**1** or **2**) to the 2- or 3-acylbenzofurans (**5** or **6**) *via* benzofurans (**3** or **4**) with 2 equivalents of NBS (Scheme 1).

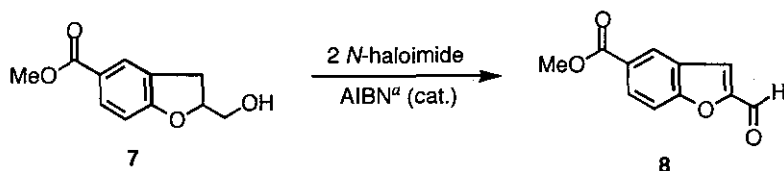
We first searched for the appropriate reaction conditions which would transform 2-hydroxymethyl-2, 3-dihydrobenzofuran (**7**)<sup>4</sup> into 2-formylbenzofuran (**8**). The results are shown in Table 1.<sup>5</sup> The reaction with NBS proceeded smoothly at 80 °C in benzene to furnish product (**8**) in moderate yield (entry 3). The reactions in other solvents such as chlorinated hydrocarbons and with other *N*-haloimides such as NCS and NIS produced low yields (entries 1, 2 and 4–6). Interestingly, the presence of additives significantly affected the yield (entries 7–14). Particularly, the addition of cyclohexene oxide raised the yield, even if the

Scheme 1



reaction was carried out in chlorinated hydrocarbons (entries 7 and 8). Thus, the use of cyclohexene oxide or potassium carbonate in benzene was the best reaction conditions (entries 9 and 10), as the additives trapped the by-product hydrogen bromide during the reaction and benzene dissolved NBS more than the chlorinated hydrocarbons.

Table 1



entry	<i>N</i> -haloimide	solvent	additive	time (min)	yield (%)
1	NBS	CCl <sub>4</sub>	none	60	<5
2	NBS	(CH <sub>2</sub> Cl) <sub>2</sub>	none	60	44
3	NBS	PhH	none	30	77
4	NCS	CCl <sub>4</sub>	none	8 h	NR <sup>b</sup>
5	NCS	PhH	none	4 h	<5
6	NIS	CCl <sub>4</sub>	none	12 h	<5
7	NBS	CCl <sub>4</sub>	C <sub>6</sub> H <sub>10</sub> O <sup>c</sup>	60	61
8	NBS	(CH <sub>2</sub> Cl) <sub>2</sub>	C <sub>6</sub> H <sub>10</sub> O	70	59
9	NBS	PhH	C <sub>6</sub> H <sub>10</sub> O	60	80
10	NBS	PhH	K <sub>2</sub> CO <sub>3</sub>	30	86
11	NBS	PhCl	C <sub>6</sub> H <sub>10</sub> O	60	72
12	NBS	PhH	Cs <sub>2</sub> CO <sub>3</sub>	20	66
13	NBS	PhH	C <sub>3</sub> H <sub>6</sub> O <sup>d</sup>	2 h	71
14	NBS	PhH	NaOAc	15	71

<sup>a</sup> 2,2'-Azobisisobutyronitrile. <sup>b</sup> 7 was recovered. <sup>c</sup> Cyclohexene oxide. <sup>d</sup> Propylene oxide.

Furthermore, we found that the 2,3-dihydrobenzofurans (9)<sup>4</sup> possessing electron-withdrawing substituents such as a nitro, halogen, methoxycarbonyl, and mesyloxy group on the benzene ring were converted to the

corresponding acylbenzofurans (**10**) in good yields under conditions similar to that described above (Table 2). Especially, the reaction of 2, 3-dihydrobenzofuran having a phenyl group in the 3-position gave a satisfactory result (entry 8). Thus, substituent groups on the benzene ring and the hydroxyalkyl groups of the 2, 3-dihydrobenzofurans (**9**) exerted no influence during the oxidation.

Table 2

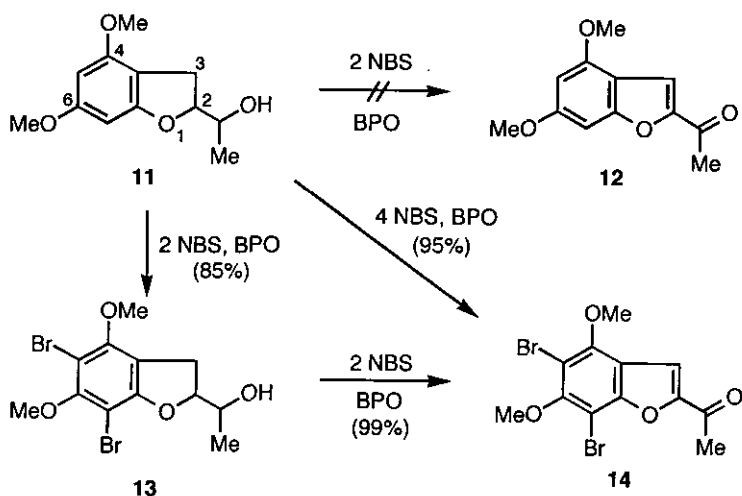
entry	substrate ( <b>9</b> )	additive	time (min)	product ( <b>10</b> )	yield (%)
1		K <sub>2</sub> CO <sub>3</sub>	50		89
2		K <sub>2</sub> CO <sub>3</sub>	30		73
3 <sup>a</sup>		C <sub>6</sub> H <sub>10</sub> O	20		87
4 <sup>b</sup>		C <sub>6</sub> H <sub>10</sub> O	10		89
5 <sup>a</sup>		C <sub>6</sub> H <sub>10</sub> O	20		79
6 <sup>b</sup>		K <sub>2</sub> CO <sub>3</sub>	2 h		83
7 <sup>b</sup>		C <sub>6</sub> H <sub>10</sub> O	20		73
8 <sup>b</sup>		C <sub>6</sub> H <sub>10</sub> O	18 h		99

<sup>a</sup> Benzoyl peroxide (BPO) was used as the radical initiator instead of AIBN. <sup>b</sup> For these entries, a diastereomeric mixture was used for the reaction. The ratio was not determined.

On the other hand, although the reaction of 4, 6-dimethoxy-2,3-dihydrobenzofuran (**11**)<sup>6</sup> possessing electron-donating groups on the benzene ring with 2 equivalents of NBS in benzene under free radical conditions did not yield the expected (**12**), the 5, 7-dibromobenzofuran derivative (**13**) was isolated in 85% yield, and **13** was converted to **14** with 2 more equivalents of NBS. When the reaction of **11** with 4 equivalents of NBS was carried out under the same conditions, **14** was expectedly formed *via* **13** in good yield (Scheme 2). Thus, 2, 3-dihydrobenzofuran (**11**) having two methoxy groups, which activate the benzene ring, is initially brominated on the benzene ring rather than at the 3-position. In a recent publication,

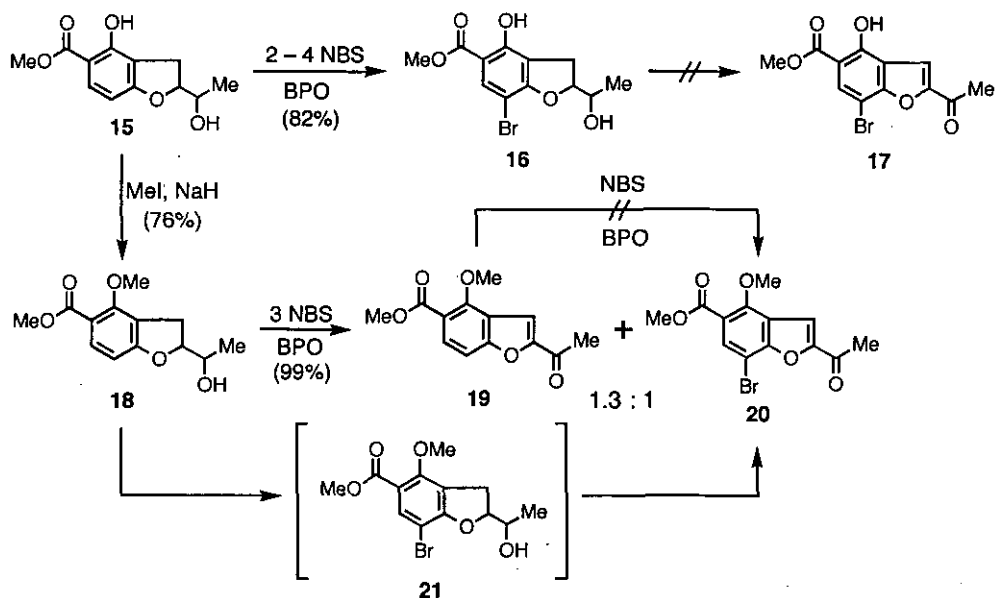
the regioselective electrophilic bromination of methyl-substituted anisoles with NBS under free radical conditions was reported.<sup>7</sup>

### Scheme 2



In another experiment, the radical reaction of 2,3-dihydrobenzofuran (**15**<sup>6</sup> or **18**) having the both of an electron-withdrawing and -donating group on the benzene ring with NBS gave the following results. The radical bromination of **15** in the 3-position with 2–4 equivalents of NBS in benzene was prevented owing to the influence of phenolic hydroxy group, and then 7-brominated compound (**16**) was obtained as a sole

### Scheme 3

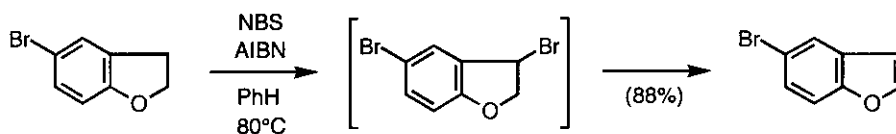


product in 82% yield, with no acylbenzofuran (**17**). Probably the phenolic hydroxy groups acts radical scavengers. On the other hand, methoxyl congener (**18**) was reacted with 3-equivalents of NBS to transform into acylbenzofuran (**19**), together with 7-bromoacylbenzofuran (**20**). These were obtained in the ratio of 1.3 : 1. The former product (**19**) was not converted to the bromide (**20**) under the same conditions and the starting material (**19**) was recovered in quantitative yield. These facts suggest that electrophilic bromination on the benzene ring in **18** takes place in competition with radical bromination in the 3-position, and that owing to influence of newly gained acetyl group in the 2-position benzene ring of **19** becomes inert to electrophilic bromination, therefore, **20** was afforded through another intermediary: 7-bromo-2, 3-dihydrobenzofuran (**21**).

In conclusion, a one-step transformation of 2- or 3-(1-hydroxyalkyl)-2, 3-dihydrobenzofurans (**1** or **2**) to the 2- or 3-acylbenzofurans (**5** or **6**) with NBS under free radical conditions has been developed. This work also provides a novel strategy for the synthesis of acylbenzofurans, since it is found that twice of the bromination-dehydrobromination process was easily achieved.

## REFERENCES AND NOTES

1. a) S. Hanessian, D. H.-c. Wong, and M. Therien, *Synthesis*, 1981, 394; b) T. Mukaiyama, M. Tsunoda, and K. Saigo, *Chem. Lett.*, 1975, 691; c) G. A. Hiegel and M. Nalbandy, *Synth. Commun.*, 1992, **22**, 1589.
2. H. B. Henbest, *J. Chem. Soc.*, 1951, 1074.
3. We confirmed that the simple 5-bromo-2,3-dihydrobenzofuran was converted to 5-bromobenzofuran in 88% yield using NBS under free radical conditions without a base.



4. General procedure for the preparation of substrates having 2-hydroxyalkyl group: H. Sato, T. Dan, E. Onuma, H. Tanaka, B. Aoki, and H. Koga, *Chem. Pharm. Bull.*, 1991, **39**, 1760. 3-hydroxyalkylated benzofurans: a) D. L. Boger and J. A. McKie, *J. Org. Chem.*, 1995, **60**, 1271; b) T. Nagashima and D. P. Curran, *Synlett*, 1995, 330.
5. Typical procedure: Under an argon atmosphere, to a stirred solution of **7** (0.48 mmol) in benzene (4 mL) was added cyclohexene oxide (1.06 mmol), NBS (1.01 mmol) and AIBN (0.005 mmol). After stirring for 60 min at 80 °C, the reaction mixture was treated with saturated NaHCO<sub>3</sub> (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane-EtOAc, 10:1) to give pure **8** (80%).
6. A diastereomeric mixture was used for the reaction. The ratio was not determined.
7. a) Y. Goldberg, C. Bensimon, and H. Alper, *J. Org. Chem.*, 1992, **57**, 6374; b) G.-J. M. Gruter, O. Akkerman, and F. Bickelhaupt, *ibid.*, 1994, **59**, 4473.

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