

A Facile Synthetic Protocol for the Preparation of 4-Halobutyl Benzoates *via* Carbon-Oxygen Bond Cleavage of THF

Jongmin Kang* and Seung-Hoi Kim

Department of Chemistry, Sejong University, Seoul 143-747, Korea

Received March 3, 2000

A facile synthetic route for the preparation of 4-halobutyl benzoates has been developed. 4-Chloro-, bromo- and iodobutyl benzoates can be easily prepared from the reaction of benzoyl chloride and metal halides in THF under extremely mild conditions. 4-Halo groups were easily controlled by selecting suitable metal halides.

A number of works for the cleavage of carbon-oxygen bond have been reported.¹ Among the previous studies, the C-O bond cleavage was observed in ether compounds, such as allyl,^{1a,1b} vinyl,^{1a,1c} crown^{1d} and aromatic ethers^{1e} in the presence of metals. Some of the resulting organometallic compounds followed by coupling with electrophiles gave the corresponding coupling compounds.² In addition to these studies, some reports exist on the C-O bond cleavage of THF.^{3,4} Among the reports mentioned above, a few studies giving 4-halobutyl alkanooates have been carried out in acid chloride and metal-catalyst system.^{3dj,k,l} Even though the exact mechanism and role of metal catalyst in this reaction system are not clear yet, Ranu^{3l} has suggested a involvement of metal halide (zinc chloride) as a complexing agent. However, it is surprising that only limited metal halides, ZnCl₂ and NaI, were frequently used. Considering the C-O bond cleavage of THF by metal halides and facile synthesis of halogenated ester derivatives which would be a interesting route to bifunctional molecules useful in organic synthesis, we explored the possibility of using a variety of different metal halides under mild conditions. As a result, various 4-halobutyl benzoates were easily obtained. Therefore, we, herein, would like to report our preliminary results of the C-O bond cleavage of THF giving 4-halobutyl benzoate in the presence of metal halide and benzoyl chloride.

The results described in Table 1 showed that in most cases where the reaction gave the corresponding product, all of the reactions were carried out under very mild conditions and resulted in good to excellent yields.

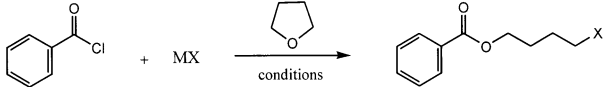
From the reactions with manganese halides (entries 1, 2 and 3), it can be inferred that the higher yield was achieved from using mild halogens. More importantly, it is also concluded that the halogen atom attached directly to the final product came from the metal halide used. For instance 4-iodobutyl benzoate was obtained by the treatment of benzoyl chloride with metal iodide (entries 3, 6, 8, 15 and 18 in Table 1). With the preliminary results from manganese halides, a variety of different metal halides have been investigated to expand this methodology. The results are summarized in Table 1. Of special interest would be the extremely mild reaction conditions. As mentioned before, most of the earlier examples were carried out in the presence of an extra solvent and/or at elevated temperature. In contrast to the works, our results have been obtained at room temperature in the

absence of any extra solvent.

The conditions used for manganese halides could be applied to most of the reactions in Table 1. Interestingly, entries 4 and 10 have been performed in milder conditions, rt/20 min. Presumably, it could be caused by the good solubility of the metal halides to THF.

In spite of the good results, some limitations have been

Table 1. Preparation of 4-halobutyl Benzoates



Entry	MX	Conditions	X ^a	Yield (%) ^b
1	MnCl ₂	rt/overnight	Cl	80
2	MnBr ₂	rt/overnight	Br	89
3	MnI ₂	rt/overnight	I	95(92 ^c)
4	ZnCl ₂	rt/20 min	Cl	89
5	LiCl	rt/overnight	Cl	75
6	Li	rt/overnight	I	87
7	CuCl	rt/overnight	Cl	72
8	KI	rt/overnight	I	85
9	CoCl ₂	rt/overnight	Cl	81
10	FeBr ₂	rt/20 min	Br	62
11	CaCl ₂	rt/overnight	—	0 ^d
12	NaBr	rt/overnight	—	0 ^d
		reflux/6 h	—	0 ^d
		rt/overnight/CH ₃ CN	—	0 ^d
13	NiBr ₂	rt/overnight	—	0 ^d
14	HgCl ₂	rt to reflux	Cl	49
15	HgI ₂	rt to reflux	I	53
16	CsCl	rt to reflux	—	0 ^d
17	RbCl	rt to reflux	—	0 ^d
18	MnI ₂ /LiI	rt/12 h	I	88
19	MnBr ₂ /LiBr	rt/overnight	Br	85
20	MnCl ₂ /LiCl	rt/48 h	Cl	47
21	<i>t</i> -BuOK	rt/2 h	—	0 ^d
22	CH ₃ C(O)SK	rt/30 min	—	0 ^d
23	HgSO ₄	rt to reflux	—	0 ^d
24	AlCl ₃	rt to reflux	—	0 ^d
25	Al(O- <i>i</i> -Pr) ₃	rt to reflux	—	0 ^d

^aProducts were fully characterized by ¹H, ¹³C NMR, FTIR and G/C-MS. ^bIsolated yield (based on benzoyl chloride) otherwise mentioned. ^c2 equivalent of benzoyl chloride was used. ^dNo product was obtained.

found in this system. As described in Table 1, reactions with some metal halides carried out under the similar conditions used before gave no coupling product (entries 11, 12, 13, 16, and 17). Most of the cases, benzoic acid was obtained instead of the coupling product.

A couple of different conditions, reflux and co-solvent, were also employed to perform the reaction shown in Table 1, entry 12. Unfortunately, the reactions were not successful.

Reactions with mixed metal halides also resulted in the coupling products, 4-halobutyl benzoates, with slightly lower yields (entries 18, 19 and 20).

With these results achieved from the reactions using metal halides, non-halogen metal complex system has been also investigated (entries 21 to 25 in Table 1). However, this system has been turned out to be ineffective.

In conclusion, a facile synthetic route to 4-halobutyl benzoates has been developed. This highly useful protocol can be readily achieved *via* C-O bond cleavage of THF in the presence of a metal halide and benzoyl chloride under mild conditions. In this system, no extra solvent was necessary to carry out the reaction. More importantly, it can be clearly inferred that the halogen atom attached to the product came from the metal halide used.

Experimental Section

The following is a representative procedure: to a solution of benzoyl chloride (5.0 mmol) in THF (5 mL) was added manganese chloride at rt and the mixture was stirred at rt overnight. After being stirred, the resulting reaction mixture was quenched with 3 N HCl solution (10 mL), extracted with ether (3 × 10 mL) and the combined organic layer was sequentially washed with saturated NaHCO₃ and NaCl solution, dried over MgSO₄. Flash chromatography (ethyl acetate/hexanes) afforded 4-chlorobutyl benzoate in 80% isolated yield.

4-Chlorobutyl benzoate.^{3h} ¹H NMR (CDCl₃) δ 8.03-7.99, 7.54-7.23 (m, 5H) 4.33 (t, *J* = 6.1 Hz, 2H), 3.24 (t, *J* = 6.3 Hz, 2H), 1.92 (m, 4H) ¹³C NMR (75 MHz, CDCl₃) δ 166.35, 132.83, 130.05, 129.38, 128.24, 63.94, 44.36, 29.10, 26.00; EIMS *m/z* 213 (M⁺).

4-Bromobutyl benzoate: ¹H NMR (CDCl₃) δ 8.08-7.42 (m, 5H), 4.36 (t, *J* = 6.0 Hz, 2H), 3.49 (t, *J* = 6.7 Hz, 2H), 2.07-1.92 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 166.49,

132.94, 130.13, 129.49, 128.34, 63.91, 33.07, 29.35, 27.35; EIMS *m/z* 257 (M⁺).

4-Iodobutyl benzoate: ¹H NMR (CDCl₃) δ 8.05-7.40 (m, 5H), 4.33 (t, *J* = 6.0 Hz, 2H), 3.24 (t, *J* = 6.0 Hz, 2H), 1.99-1.85 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 166.35, 132.81, 130.00, 129.38, 128.23, 63.58, 29.91, 29.49, 5.96; EIMS *m/z* 305 (M⁺).

Acknowledgment. We thanks for the financial support from Korea Ministry of Science and Technology.

References and Note

- Recent examples, see; (a) Deelman, B.-J.; Booij, M.; Meetsma, A.; Teuben, J. H.; Kooijman, H.; Spek, A. L. *Organometallics* **1995**, *14*, 2306 and references cited therein. (b) Takaki, K.; Kusudo, T.; Uebori, S.; Makioka, Y.; Tanigudri, Y.; Fujiwara, Y. *Tetrahedron Lett.* **1995**, *36*, 1505. (c) Takaki, K.; Maruo, M.; Kamata, T.; Makioka, Y.; Fujiwara, Y. *J. Org. Chem.* **1996**, *61*, 8332. (d) Sokol, M.; Kowalczyk, M.; Grobleny, Z.; Janeczka, H.; Jedlinski, Z.; Luboch, E.; Biernat, J. *J. Org. Chem.* **1995**, *60*, 2365 and references cited therein. (e) Fish, R. H.; Dupon, J. W. *J. Org. Chem.* **1988**, *53*, 5230.
- Takaki, K.; Kusudo, T.; Uebori, S.; Nishiyama, T.; Kamata, T.; Yokoyama, M.; Takehira, K.; Makioka, Y.; Fujiwara, Y. *J. Org. Chem.* **1998**, *63*, 4299 and references cited therein.
- (a) Kulkarni, S. U.; Patil, V. D. *Heterocycles* **1982**, *18*, 163. (b) Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 3969. (c) Goldsmith, D. J.; Kennedy, E.; Campbell, R. G. *J. Org. Chem.* **1975**, *40*, 3571. (d) Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681. (e) Node, M.; Kajimoto, T.; Nishide, K.; Fujita, E.; Fuji, K. *Tetrahedron Lett.* **1984**, *5*, 219. (f) Amouroux, R.; Jaiczak, M.; Chastrette, M. *Bull. Soc. Chim. Fr.* **1987**, *3*, 505. (g) Pri-Bar, I.; Stille, J. K. *J. Org. Chem.* **1982**, *47*, 1215. (h) Fitch, J. W.; Payne, W. G.; Westmoreland, D. *J. Org. Chem.* **1983**, *48*, 751. (i) Karger, M. H.; Mazur, Y. *J. Am. Chem. Soc.* **1968**, *90*, 3878. (j) Morrell, S. S. *Chem. Abstr.* **1947**, *41*, 7411. (k) Minceco, P.; Saluzzo, C.; Amouroux, R. *Tetrahedron Lett.* **1994**, *35*, 1553. (l) Bhar, S.; Ranu, B. C. *J. Org. Chem.* **1995**, *60*, 745.
- Freijee, F.; Schat, G.; Mierop, R.; Blomberg, C.; Bickelhaupt, F. *Heterocycles* **1977**, *7*, 237.
- Amouroux proposed the *in-situ* formation of the corresponding acid halides from the acid chloride and metal halide; see, ref. 3k.