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Tetrahydrofuran Ring-opening with Acyloxyphosphonium Bromide Catalyzed by Zinc Bromide: An Effective Method for the Preparation of 4-Bromobutyl Esters

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Abstract: Catalyzed by zinc bromide, tetrahydrofuran ring can be opened with acyloxyphosphonium bromide generated *in situ* to afford 4-bromobutyl esters under mild conditions in good to excellent yields.

Keywords: Zinc bromide, tetrahydrofuran ring, acyloxyphosphonium bromide, 4-bromobutyl esters.

Tetrahydrofuran ring-opening with acyl halides or acid anhydrides is a useful method for preparation of 4-halobutyl esters[1]. As a result, several methods have been reported for this purpose. For example, the reaction of tetrahydrofuran with sodium iodide and acid chlorides[2], the tetrahydrofuran ring-opening with acid chlorides or acid anhydrides catalyzed by samarium triiodide[3,4] to give 4-iodobutyl esters; the acylative ring-opening of tetrahydrofuran with acid chlorides catalyzed by yttrium trichloride[5], titanium chloride or stannic chloride[6] to produce 4-chlorobutyl esters, *etc*. However, all of these procedures are only restricted to acyl chlorides or acid anhydrides, which are not easy to prepare, handle and purify. Besides, comparison with 4-iodobutyl and 4-chlorobutyl esters, less attention was paid to synthesize 4-bromobutyl esters since acyl bromides are even more difficult to prepare than acyl chlorides[7]. In a word, there is still considerable interest in finding more convenient and effective method for synthesis of 4-halobutyl esters.

In the last decades, acyloxyphosphonium salts have been reported as a new type of acylating reagents. Such species could be generated *in situ* by treatment of a mixture of a carboxylic acid and triphenylphosphine with tetrahalomethane[8], NBS or NCS[9]. The application of them to synthesize amides[8,9,10], esters[11] and acyl azides[12] have been reported. However, all such reactions were not atom economic since the halide anions of the acyloxyphosphonium salts were not utilized. Herein, we wish to report that tetrahydrofuran ring opening reaction with acyloxyphosphonium bromide to yield 4-bromobutyl esters (**Scheme**).

We have modified the procedure for preparation of acyloxyphosphonium bromide **1**, directly mixing a sodium carboxylate, triphenylphosphine and bromine in CH_2Cl_2 in order to avoid the by-products trihalomethane by Yamada's procedure[8] and N-

succinimide by Frøyen's procedure[9]. 10 mol% $ZnBr_2$ was used as the catalyst, only 4-bromobutyl esters were obtained in good to excellent yields. The results were summarized in **Table** . All new products were characterized by IR, MS, ^1H NMR and elemental analysis[14].

Scheme

$$RCOONa \xrightarrow[CH_2Cl_2,\ r.t.]{Ph_3P\bullet Br_2} [\ RCOO\overset{+}{P}Ph_3Br^-\ ] \quad \mathbf{1}$$

$$[\ RCOO\overset{+}{P}Ph_3Br^-\ ] \ (\mathbf{1}) + \text{tetrahydrofuran} \xrightarrow[CH_2Cl_2,\ r.t.]{10\%\ ZnBr_2} RCOOCH_2(CH_2)_2CH_2Br + Ph_3P{=}O \quad \mathbf{2a\sim j}$$

2a. R=Ph; **2b**. R=*p*-$CH_3C_6H_4$; **2c**. R=*p*-$CH_3OC_6H_4$; **2d**. R=*p*-ClC_6H_4; **2e**. R=*m*-ClC_6H_4; **2f**. R=*p*-IC_6H_4; **2g**. R=*p*-$NO_2C_6H_4$; **2h**. R=(E)-PhCH=CH; **2i**. R=CH_3; **2j**. R=1-napthylmethyl

We found that the intermediate **1** was chemically very reactive. The opening of tetrahydrofuran was usually completed in short times with catalyst $ZnBr_2$ even at room temperature. If there was no catalyst the reaction needed longer time and afforded lower yield. A variety of sodium carboxylate were suited for preparation of **1**. The **Table** shows that sodium salts of aromatic carboxylic acid could obtain excellent yields while aliphatic ones gave lower yields. When sodium cinnamate (E form) was used, the reaction could also afford desired yield. Substituents on the aromatic ring such as chloro, bromo, iodo, methyl, methoxy, or nitro groups were not affected the reaction.

Table Tetrahydrofuran ring opening reaction with acyloxyphosphonium bromide catalyzed by $ZnBr_2$

Entry	R	Reaction time (h)	Yield (%)[a]
2a	Ph	5	62[b]
2a	Ph	1	94[c]
2a	Ph	1	93[14]
2b	*p*-$CH_3C_6H_4$	1	94
2c	*p*-$CH_3OC_6H_4$	1	91
2d	*p*-ClC_6H_4	1	91
2e	*m*-ClC_6H_4	2.0	90
2f	*p*-I C_6H_4	1	92
2g	*p*-$NO_2C_6H_4$	1	90[14]
2h	(E)-PhCH=CH	1.5	87
2i	CH_3	5	76[14]
2j	1-napthylmethyl	4	78

[a]Isolated yield. [b]Reaction was carried out without addition of catalyst. [c]Mixture of 4-bromobutyl esters and 4-chlorobutyl esters (79% of the former and 15% of the latter determined by 300 MHz NMR) when 10 mol% $ZnCl_2$ was used as the catalyst.

In conclusion, it has been found that tetrahydrofuran ring could be efficiently opened with acyloxyphosphonium bromide catalyzed by $ZnBr_2$ to give 4-bromobutyl esters in good to excellent yields. The notable advantages of the present procedure are mild conditions, easy availability of starting materials, simple operation, short reaction time, atom economy and good to excellent yields.

Experimental

Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately *prior to* use. CH_2Cl_2 was purified and dried by the standard procedure before use. All reactions were conducted under nitrogen atmosphere.

General procedure for tetrahydrofuran ring-opening reaction with acyloxyphosphonium bromide catalyzed by $ZnBr_2$:

To a stirred solution of triphenylphosphine (0.26 g, 1.0 mmol) and bromine (0.16 g, 1 mmol) in anhydrous dichloromethane (10 mL) at room temperature was added sodium carboxylate (1.0 mmol) in one portion. The mixture was stirred for 30 min at room temperature until the colour of the mixture turned to yellow which indicated that acyloxyphosphonium bromide was formed. Then to the solution were added $ZnBr_2$ (0.023 g, 0.1 mmol) and THF(1.0 mmol). The resulting mixture was further stirred for given time (**Table**) at room temperature. Water (5 mL) was added to quench the reaction and the mixture was extracted with diethyl ether (2×30 mL). The extracts were washed with saturated sodium thiosulfate (5 mL) and brine. After the solution was dried over anhydrous Na_2SO_4, the solvents was removed under reduced pressure; the residue was then purified by preparative TLC on silica gel with cyclohexane-ethyl acetate (12:1) as eluent.

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14. **2a**: bp: 177-178°C /14mmHg (lit.[13]: 176-178°C /14mmHg). **2b**: Oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.92 (d, 2H, J=8.2Hz, ArH), 7.22 (d, 2H, J=8.2Hz, ArH), 4.32 (t, 2H, J=6.2 Hz, OCH_2), 3.44 (t, 2H, J=6.5 Hz, CH_2Br), 2.38 (s, 3H, CH_3), 2.02-1.88 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1720 (C=O); MS *m/z* (%): 271 (M^+, 15.92), 273 (M^++2, 15.65). Anal. calcd. for $C_{12}H_{15}BrO_2$: C 53.16; H 5.58. Found: C 53.27; H 5.64. **2c**: Oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.97 (d, 2H, J=8.8Hz, ArH), 6.89 (d, 2H, J=8.8Hz, ArH), 4.30 (t, 2H, J=6.2 Hz, OCH_2), 3.82 (s, 3H, CH_3), 3.46 (t, 2H, J=6.5 Hz, CH_2Br), 2.02-1.88 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1712 (C=O); MS *m/z* (%): 286 (M^+, 7.54), 288 (M^++2, 7.35). Anal. calcd. for $C_{12}H_{15}BrO_3$: C 50.19; H 5.26. Found: C 50.30; H 5.19. **2d**: Oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.95 (d, 2H, J=8.6Hz, ArH), 7.39 (d, 2H, J=8.6Hz, ArH), 4.34 (t, 2H, J=6.2 Hz, OCH_2), 3.46 (t, 2H, J=6.5 Hz, CH_2Br), 2.03-1.90 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1721 (C=O); MS *m/z* (%): 291 (M^+, 5.04), 293 (M^++2, 4.93). Anal. calcd. for $C_{11}H_{12}BrClO_2$: C 45.31; H 4.15. Found: C 45.23; H 4.20. **2e**: Oil;

^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.99-7.89 (m, 2H, ArH), 7.51-7.35 (m, 2H, ArH), 4.35 (t, 2H, J=6.2 Hz, OCH_2), 3.48 (t, 2H, J=6.5 Hz, CH_2Br), 2.04-1.92 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1721 (C=O); MS *m/z* (%): 291 (M^+, 2.47), 293 (M^++2, 2.36). Anal. calcd. for $C_{11}H_{12}BrClO_2$: C 45.31; H 4.15. Found: C 45.42; H 4.21. **2f**: Oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.78 (d, 2H, J=8.6Hz, ArH), 7.72 (d, 2H, J=8.6Hz, ArH), 4.34 (t, 2H, J=6.2 Hz, OCH_2), 3.46 (t, 2H, J=6.5 Hz, CH_2Br), 2.03-1.90 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1718 (C=O); MS *m/z* (%): 382 (M^+, 13.11), 384 (M^++2, 13.43). Anal. calcd. for $C_{11}H_{12}BrIO_2$: C 34.49; H 3.16. Found: C 34.54; H 3.19. **2g**: bp: 190-193°C (lit.[7]: 191-194°C). **2h**: Oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.68 (d, 1H, J=16Hz, ArCH=), 7.52-7.50 (m, 2H, ArH), 7.40-7.35 (m, 3H, ArH), 6.43 (d, 1H, J=16Hz, $=CHCO_2$), 4.23 (t, 2H, J=6.2 Hz, OCH_2), 3.45 (t, 2H, J=6.5 Hz, CH_2Br), 2.02-1.84 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1713 (C=O), 1637 (C=C); MS *m/z* (%): 282 (M^+, 6.85), 284 (M^++2, 6.92). Anal. calcd. for $C_{13}H_{15}BrO_2$: C 55.14; H 5.34. Found: C 55.05; H 5.28. **2i**: bp: 94-96°C (lit.[7]: 95-96°C). **2j**: Oil; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.95-7.15 (m, 7H, ArH), 4.03-3.97 (m, 4H, $ArCH_2$, $COOCH_2$), 3.20 (t, 2H, J=6.3 Hz, CH_2Br) 1.67-1.57 (m, 4H, $(CH_2)_2$); IR (film/CCl_4, cm^{-1}): 1734 (C=O); MS *m/z* (%): 320 (M^+, 12.34), 322 (M^++2, 12.56). Anal. calcd. for $C_{16}H_{17}BrO_2$: C 59.83; H 5.33. Found: C 59.67; H 5.25.

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