2500 BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 49 (9), 2500—2502 (1976) [Vol. 49, No. 9

Reaction of Alkyl Halides with Mercury(II) Salts in Tetrahydrofuran. A Facile Preparation of 4-Alkoxybutyl Acetates and Chlorides

Nanao WATANABE, Sakae UEMURA,* and Masaya OKANO*,**
Koei Chemical Co., Ltd., Joto-ku, Osaka 536
**Institute for Chemical Research, Kyoto University, Uji, Kyoto 611*

(Received December 12, 1975)

The reaction of primary and secondary alkyl iodides and bromides with $Hg(OAc)_2$ and $HgCl_2$ in tetrahydrofuran (THF) affords the THF-incorporated compounds (**1**), $RO(CH_2)_4X$ [X=OAc and Cl, respectively], in good yields. When $HgBr_2$ and aqueous or alcoholic $Hg(ClO_4)_2$ were used as mercury(II) salts, the yields of **1**(X=Br, OH, and OR′) were low. Similar treatment with HgI_2 gave scarcely any **1**. A reaction scheme which involves *O*-alkyltetrahydrofuranium ion as the intermediate is proposed for the formation of **1**.

Reactions of alkyl halides with mercury(II) salts are of current interest.1—5) In a previous paper5) we showed that primary and secondary alkyl halides react with $Hg(SCN)_2$ in THF to give the THF-incorporated compounds, $R[O(CH_2)_4]_nNCS(-SCN)$ ($n=1$, 2), the reaction proceeding through *O*-alkyltetrahydrofuranium ion intermediate. During the course of application of this reaction to various other mercury(II) salts we found that the reaction using mercury(II) acetate and chloride gives $RO(CH_2)_4X$ (X=OAc and Cl) in good yields. Although the direct replacement of the halogen atom in alkyl halides by the carboxyl moiety of mercury(II) salts of carboxylic acids in THF or other organic solvents has been reported,2) no description is given on the formation of such a THF-incorporated compound. In the present paper we describe the results of the reaction with various mercury(II) salts and discuss its reaction scheme.

TABLE 1. REACTION OF RX WITH $Hg(OAc)_2$ OR $HgCl_2$ IN THF

(A) With $Hg(OAc)_2$$^{a)}$

RX	React temp (°C)	React time (h)	Yields (%)$^{b)}$ 1 (n=1)	1 (n=2)	2
EtI	70—75	7	68	5	22
n-PrI	70—75	7	66	—$^{c)}$	30
i-PrI	70—75	5	50	3	35
i-PrBr	60—65	8	45	—	29
n-BuI	70—75	7	68	3	29
s-BuBr	70—75	8	37	—	29
CH_2=$CHCH_2Br$	70—75	2.5	62	8	17
$PhCH_2Br$	65—68	7	40$^{d)}$	—	42$^{d)}$
t-BuBr	70—72	4	0	0	45$^{d)}$
PhCH(Me)Br	45—48	2	0	0	90$^{d)}$

(B) With $HgCl_2$$^{a)}$

RX	React temp (°C)	React time (h)	Yields (%)$^{b)}$ 1 (n=1)	1 (n=2)	2
EtI	70—75	6	68	14	—$^{c)}$
i-PrI	70—75	7	68	2	—
n-BuI	70—75	7	70	9	8
CH_2=$CHCH_2Br$	70—75	2	56	8	21
$PhCH_2Br$	60—65	1	19$^{d)}$	—	67$^{d)}$

a) RX, 20 mmol. HgZ_2, 20 mmol. THF, 15 ml. b) Determined by GLC. c) Not determined. d) Isolated yield.

Results and Discussion

Reaction with $Hg(OAc)_2$ or $HgCl_2$. The reaction was carried out by stirring alkyl iodides or bromides and mercury(II) salts in THF at refluxing temperature for several hours. The products were the THF-incorporated compounds (**1**) and the expected substitution products (**2**) (Scheme 1). From primary and secondary alkyl iodides or bromides, **1** ($n=1$) was mainly obtained, while alkyl bromides having strong S_N1 characteristics such as *t*-butyl and α-methylbenzyl bromides reacted to give only **2**. Typical results are summarized in Table 1. Predominant formation of **1** ($n=1$) with small amounts of **1** ($n=2$) was characteristic especially in the case of $Hg(OAc)_2$, in contrast to the reaction with $Hg(SCN)_2$ where both **1** ($n=1$) and **1** ($n=2$) were formed as main products.5) Alkyl chlorides scarcely reacted under the conditions shown in Table 1.

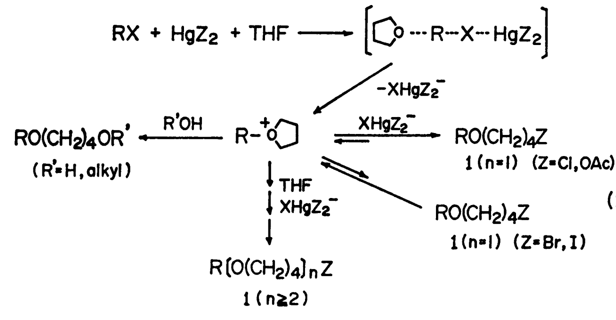
$$RX + HgZ_2 + THF \longrightarrow \underset{\mathbf{1}\ (n=1,\,2)}{R[O(CH_2)_4]_nZ} + \underset{\mathbf{2}}{RZ} \qquad (1)$$

Reaction with $HgBr_2$, HgI_2, or $Hg(ClO_4)_2$. The reaction with $HgBr_2$ or HgI_2 under similar conditions to those described above gave mainly high-boiling substances which seemed to be **1** ($n \geqq 2$). As an example, from the reaction of ethyl iodide with $HgBr_2$ for 2 h, **1** ($n=1$) was obtained in 26% yield together with large amounts of high-boiling substances. When the reaction was continued for an additional 4 h, the yield of **1** ($n=1$) decreased to 10%. In the case of HgI_2, **1** ($n=1$) was obtained only in a very low yield, high-boiling substances being mainly formed even under milder reaction conditions. All the starting alkyl halide was consumed in all the cases. On the other hand, the reaction with $Hg(ClO_4)_2$ in THF containing water or an alcohol afforded **1** ($n=1$) and **2** where Z=OH or OR′ in good yields, only small amounts of high-boiling substances being formed in this case (see Experimental).

Reaction Scheme. Because of the similarity of the products to those in the reaction with $Hg(SCN)_2$,5) the reaction seems to proceed through a scheme involving an oxonium ion intermediate as has been proposed in the case of $Hg(SCN)_2$ (Scheme 2). If no considerable competing attacks on this intermediate cation by another THF molecule and by some other nucleophiles

---

** To whom correspondence should be addressed.



(2)

such as water or an alcohol take place, almost exclusive formation of $RO(CH_2)_4Z$ or $RO(CH_2)_4X$ by the S_N2-like attack of $XHgZ_2^-$ where X=I or Br and Z=Cl, OAc, Br, or I should be expected. Here, in the cases of Z=Cl, OAc, and Br a favorable attack by Z can occur to give only $RO(CH_2)_4Z$ because the affinity of I to Hg^{2+} is much greater than that of Cl, OAc, and Br to it by considering HSAB principle[6] (Hg^{2+} is a soft acid; Cl^- and OAc^- are hard bases, Br^- is a borderline base, and I^- is a soft base). In view of the fact that the yields of **1** ($n=1$) were low and considerable amounts of high-boiling substances were formed in the cases of Z=Br and I, the stability of the products, **1** ($n=1$), under the reaction conditions should also be taken into consideration. We have observed in these cases that a longer reaction time resulted in the formation of high-boiling substances which are probably composed of many THF molecule inserted compounds, **1** ($n>2$). It has been found that the reaction of $RO(CH_2)_4Br$ with $Hg(SCN)_2$ proceeds rapidly to give $RO(CH_2)_4NCS$ and $RO(CH_2)_4SCN$ *via* *O*-alkyltetrahydrofuranium ion.[5] This indicates that the reverse reaction from **1** ($n=1$) to the oxonium ion occurs in the presence of a mercury(II) salt, its extent depending a great deal on the kind of Z. The ease of departure of the leaving groups (Z) in S_N1 reaction is known to decrease in this order: I>Br>OAc>OH,OR.[7]

TABLE 2. REACTION OF $EtO(CH_2)_mBr$ WITH HgZ_2 IN n-Bu_2O[a]

m	Z	React temp (°C)	React time (h)	EtO-$(CH_2)_mZ$ Yield (%)[b]	EtO-$(CH_2)_mBr$ Recovered (%)[b]
2	Cl	70—75	8	0	99
3	Cl	70—75	8	0	92
4	Cl	70—75	8	89	trace
4	OAc	65—70	2	13	80
4	OAc	70—78	7	81	15
5	Cl	70—78	8	7	61

a) $EtO(CH_2)_m Br$, 10 mmol. HgZ_2, 10 mmol. n-Bu_2O, 8 ml. b) Determined by GLC.

In order to confirm the above explanation, the reaction of $EtO(CH_2)_mBr$ (m=2—5) with $HgCl_2$ or $Hg(OAc)_2$ was carried out with n-Bu_2O as a solvent. The results are given in Table 2. As expected, when m=4 thermodynamically more stable $EtO(CH_2)_4Cl$ or $EtO(CH_2)_4OAc$ was obtained in a good yield, while no reaction occurred when m=2 and 3 in accordance with a similar result by Winstein *et al.*[8] We also confirmed that the reaction of $EtO(CH_2)_4Cl$ with $HgBr_2$ in n-Bu_2O gave no $EtO(CH_2)_4Br$ under the conditions shown in Table 2 and that of $EtO(CH_2)_4Br$ with HgI_2 in THF gave readily a lot of high-boiling substances.

Experimental

GLC analyses were carried out on a Yanagimoto G800-T and a Shimadzu 5APTF apparatus using DEGS (1m), PEG 6000 (2 and 3m), and EGSS-X (1m) columns (carrier gas, H_2 and N_2 respectively). The NMR spectra were recorded with Varian EM-360 and JEOL MH-100 spectrometers in $CDCl_3$, using TMS as an internal standard. The IR and Mass spectra were taken with Hitachi EPI-S2 and JEOL JMS-01SG spectrometers, respectively.

Materials. All the organic substances, including the solvents, were used after distillation, while commercial inorganic salts were used without further purification. ω-Ethoxyalkyl bromides, $EtO(CH_2)_mBr$, were prepared by the reported method.[9] Authentic samples of **1** ($n=1$, Z=OAc) were prepared by the acetylation of 4-alkoxybutanol synthesized[9] from 1,4-butandiol, sodium, and alkyl bromide. Authentic samples of **1** ($n=1$, Z=Cl) were prepared by the reported method; thus $PhCH_2O(CH_2)_4Cl$ was prepared from benzyl chloride, THF, and $ZnCl_2$,[10] and n-$BuO(CH_2)_4Cl$ from n-$BuO(CH_2)_4OH$ and $SOCl_2$.[11] Commercial authentic samples of **2** were used.

Reaction of Alkyl Halides with $Hg(OAc)_2$ or $HgCl_2$ in THF (Table 1). The following example shows a typical procedure. To a suspension of $Hg(OAc)_2$ (12.8 g, 40 mmol) in THF (30 ml) was added n-PrI (6.8 g, 40 mmol) at 70—75 °C and the resulting homogeneous solution was kept for 7 h under stirring. After being cooled down to room temperature, Et_2O (300 ml) was added and the precipitated inorganic salt was filtered off. The filtrate was washed several times with aqueous KI in order to remove a small amount of dissolved mercury (II) salt and then dried over $MgSO_4$. Distillation gave two fractions, D_1 (propyl acetate, 0.58 g, bp 50—75 °C) and D_2 (4-propoxybutyl acetate, 3.53 g, bp 101—104 °C/20 mmHg), and left 0.2 g of residue.

The boiling points (°C/mmHg) of **1** ($n=1$, Z=OAc) are as follows: R=Et, 90—91/24 (lit,[12] 192—193/756); R=i-Pr, 93—95/20; R=n-Bu, 118—120/25; R=s-Bu, 105—108/24; R=allyl, 104—106/24; R=benzyl, 112—115/2. Those of **1** ($n=1$, Z=Cl) are as follows; R=Et, 56—57/19 (lit,[13] 142/760); R=i-Pr, 71—73/25; R=n-Bu, 94—95/22 (lit,[11] 84/13); R=allyl, 90—92/35; R=benzyl, 102—104/1 (lit,[10] 137—140/12). **1** ($n=2$ Z=OAc), R=Et, 120—122/2. **1** ($n=2$, Z=Cl), R=Et, 120—125/7; R=i-Pr, 88—90/1; R=n-Bu, 127—128/4. NMR, IR, and mass spectra of all compounds support the structures. Although some of **1** ($n=2$) could not be isolated in a pure state, the retention time in GLC and NMR spectra supports each structure.

Reaction of n-*BuI with Aqueous $Hg(ClO_4)_2$ in THF.* Red mercury(II) oxide (4.4 g, 20 mmol) was added to a mixture of THF (15 ml) and 60% $HClO_4$ (6.8 g, 40 mmol), and the mixture was gently heated on a water bath (40—60 °C) under stirring until almost all the mercury(II) salt has dissolved (10—20 min). After being cooled down to room temperature, 4 ml of water and 3.7 g (20 mmol) of n-BuI were added to the mixture which was then stirred at 40 °C for 4 h. The products were then analyzed directly by GLC by use of internal standards: n-BuOH, 0.76 g (10.3 mmol), 51% yield: n-$BuO(CH_2)_4OH$, 0.90 g (6.2 mmol), 31%; n-$BuO(CH_2)_4O$-n-Bu, 0.36 g (1.8 mmol), 9%. An authentic sample of n-$BuO(CH_2)_4O$–n-Bu was prepared from n-$BuO(CH_2)_4Br$, n-BuOH, and sodium; bp 138—139 °C/40 mmHg (lit,[14] 234—236 °C/760 mm-

Hg). Distillation left only a small amount of residue ($<$0.05 g).

Reaction of n-*BuI with Alcoholic $Hg(ClO_4)_2$ in THF.* To a mercury(II) perchlorate (20 mmol) solution of THF prepared by the same method as described above was added 15 g of *n*-BuOH and 3.7 g (20 mmol) of *n*-BuI. The mixture was then stirred at 40 °C for 4 h. After being cooled down to room temperature, Et_2O (200 ml) was added and the precipitated inogranic salt was filtered off. The filtrate was washed with aq. KI and dried. After evaporation of ether, the products in residue were analyzed by GLC by using some internal standards: *n*-Bu_2O, 1.23 g (9.5 mmol), 47%; *n*-$BuO(CH_2)_4O$-*n*-Bu, 0.96 g (4.8 mmol), 24%; *n*-$BuO(CH_2)_4OH$, 0.23 g (1.6 mmol), 8%. Distillation left only a small amount of residue ($<$0.05 g).

Reaction of $EtO(CH_2)_mBr$ with $HgCl_2$ or $Hg(OAc)_2$ in n-*Bu_2O. (Table 2).* A typical procedure is given in the following. To a suspension of $HgCl_2$ (2.8 g, 10 mmol) in *n*-Bu_2O (8 ml) was added $EtO(CH_2)_5Br$ (1.95 g, 10 mmol) at 70—75 °C and the resulting mixture was kept for 8 h under stirring. After being cooled down to room temperature, the mixture was filtered from the solid part and the filtrate was analyzed by GLC: recovered $EtO(CH_2)_5Br$, 1.19 g (6.1 mmol), 61%; $EtO(CH_2)_5Cl$, 0.11 g (0.7 mmol), 7%. An authentic sample of $EtO(CH_2)_5Cl$ was prepared by action of $SOCl_2$ on $EtO(CH_2)_5OH$ in pyridine; bp 88 °C/43 mmHg (lit,[13] 72 °C/17 mmHg).

References

1) N. Watanabe, M. Okano, and S. Uemura, *Bull. Chem. Soc. Jpn.*, **47**, 2745 (1974).

2) R. C. Larock, *J. Org. Chem.*, **39**, 3721 (1974).

3) A. McKillop and M. E. Ford, *Tetrahedron*, **30**, 2467 (1974).

4) J. S. Filippo, Jr. and L. J. Romano, *J. Org. Chem.*, **40**, 782 (1975).

5) N. Watanabe, S. Uemura, and M. Okano, *Bull. Chem. Soc. Jpn.*, **48**, 3205 (1975).

6) R. G. Pearson, *Chem. Brit.*, **3**, 103 (1967).

7) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston Inc., New York, N. Y. (1959), p. 261.

8) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

9) L. I. Smith and J. A. Sprung, *J. Am. Chem. Soc.*, **65**, 1276 (1943).

10) G. G. Munoz and R. Madronero, *Chem. Ber.*, **95**, 2184 (1962).

11) P. Rempp, *Bull. Soc. Chim. Fr.*, **1957**, 844.

12) A. Dewael, *Bull. Soc. Chim. Belges*, **35**, 302 (1926).

13) P. M. Frearson and E. S. Stern, *J. Chem. Soc.*, **1958**, 3064.

14) T. P. Hobin, *Polymer*, **6**, 407 (1965).