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A Practical Synthesis of 3-Chloro-α-Bromostyrene Starting from 3-Chloroethylbenzene

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ABSTRACT: 3-Chloro-α,β-dibromoethylbenzene was prepared via I_2 catalyzed bromination of 3-chloro-α-bromoethylbenzene. It was dehydrobrominated with aqueous NaOH in the presence of n-$Bu_4N^+HSO_4^-$ to give 3-chloro-α-bromostyrene in 92% overall yield.

α-Bromostyrene derivatives are important starting materials for the synthesis of 2-phenyl-2-propen-1-ol derivatives.[1] In particular, 3-chloro-α-bromostyrene **1** is a key intermediate for the synthesis of MK-243,[2] which is a potent herbicide used for rice plants.[3] Until now, two main convenient approaches have been documented for the synthesis of α-bromostyrene derivatives. One is the reaction of acetophenone derivatives with PBr_3[4] and the other is the dehydrobromination of α,β-dibromoethylbenzene derivatives with NaOH-EtOH.[5] α,β-Dibromoethylbenzene derivatives are prepared by the reaction of styrene derivatives with Br_2[6] and

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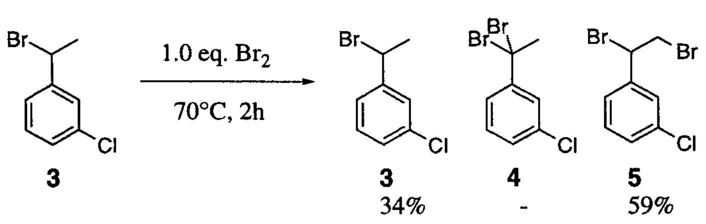
the reaction of ethylbenzene derivatives with PhCH$_2$N$^+$Me$_3$Br$_3^-$ in the presence of 2,2'-azobis(isobutyronitrile)[7] or Br$_2$ in the presence of Et$_4$N$^+$Br$^-$.[8] However, the existing methods are not applicable for a large scale preparation of **1**, because 3-chloroacetophenone, 3-chlorostyrene, and PhCH$_2$N$^+$Me$_3$Br$_3^-$ are expensive raw materials, the use of PBr$_3$ produces large amount of phosphoric acid waste, and the simultaneous aromatic bromination occurred in the reaction of ethylbenzene derivatives with Br$_2$ in the presence of Et$_4$N$^+$Br$^-$. In this paper, we wish to report a practical one-pot preparation of 3-chloro-α-bromostyrene in an excellent yield from commercially available and cheap 3-chloroethylbenzene **2**, which is easily manufactured via ethylation of chlorobenzene[9] or isomerization of chloroethylbenzene in the presence of Friedel-crafts catalysts such as AlCl$_3$[10] and zeolite.[11]

It is well known that the reaction of α-bromoethylbenzene with Br$_2$ in the presence of radical initiators gives α,α-dibromoethylbenzene.[12] But, surprisingly, when 3-chloro-α-bromoethylbenzene **3** was reacted with 1.0 equivalent of Br$_2$ at 70°C, the reaction gave 3-chloro-α,β-dibromoethylbenzene **5** in 59% yield (Scheme 1).



Scheme 1

Reactions of **3** with Br$_2$ were examined under various reaction conditions to increase the yield of **5** (Table 1). The use of solvents decreased the yield of **5**

(Entry 1-2). Among the catalysts examined, the use of 0.01 equivalent of I_2 was effective to increase the reaction rate (Entry 6). Under this condition, aromatic bromination products were not detected. When **3** was reacted with 1.5 equivalents of Br_2 in the presence of 0.0025 equivalent of I_2 without solvent at 70°C for 2 hr, the dibromide **5** was obtained in 95% yield (Entry 8).

Table 1. Reactions of **3** with Br_2 in Various Reaction Conditions[a)]

Entry	Solvent[b)]	Catalyst	Catalyst (eq.)	Br_2 (eq.)	Time (h)	Yield[c)] **5** (%)
1	CCl_4	-	-	1.0	4.0	3
2	cyclohexane	-	-	1.0	4.0	3
3	-	-	-	1.0	2.0	59
4	-	$PhCH_2N(CH_3)_3^+Cl^-$	0.01	1.0	2.0	61
5	-	$n\text{-}Bu_4N^+HSO_4^-$	0.01	1.0	2.0	61
6	-	I_2	0.01	1.0	2.0	77
7	-	I_2	0.01	1.5	2.0	95
8	-	I_2	0.0025	1.5	2.0	95

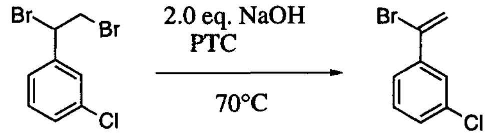
a) 10 g (33.5 mmol) of **3** was used. Reactions were carried out at 70°C.
b) Solvent / **3** = 5 / 1 (Volume (ml) / Weight (g)).
c) Yields were based on **3**.

Next, the dehydrobromination of **5** with aqueous NaOH was investigated in the presence of various phase transfer catalysts (PTC) to produce vinyl bromide **1** (Table 2). Among those examined, the use of $n\text{-}Bu_4N^+HSO_4^-$ allowed the short reaction time and the use of low concentration of aqueous NaOH (Entry 5-7).

One-pot preparation of **1** from **2** was shown in Scheme 2. That is, **2** was reacted with 1.0 equivalent of Br_2 in the presence of 0.0001 equivalent of 2,2'-azobis(isobutyronitrile) at 50-60°C and successively reacted with 1.5 equivalents of Br_2 in the presence of 0.0025 equivalent of I_2 at 70°C to afford crude dibromide **5**. The crude **5** was quenched with 25% aqueous $NaHSO_3$ at 40°C and successively reacted with 25% aqueous NaOH in the presence of 0.005 equivalent of *n*-$Bu_4N^+HSO_4^-$ at 70°C to give **1** in 92% overall yield.

In conclusion, the one-pot preparation of **1**, a key intermediate of MK-243, starting from **2** was accomplished in an excellent yield. This method employs readily available materials and simple operations and is also applicable to industrial scale preparation.

Table 2. Dehydrobromination of **5** Using Various PTC[a)]



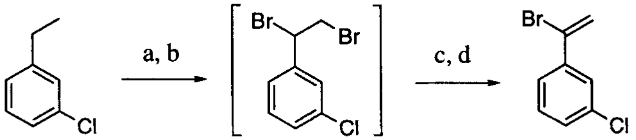
5 **1**

Entry	PTC	PTC (eq.)	Conc. of NaOH aq. (%)	Time (h)	Conv. of 5 (%)	Yield[b)] 1 (%)
1	$Me_4N^+Cl^-$	0.01	25	6	28	13
2	$Bu_4N^+Br^-$	0.01	25	6	87	77
3	$PhCH_2N(CH_3)_3^+Cl^-$	0.01	25	6	99	92
4	$PhCH_2N(CH_3)_3^+Cl^-$	0.01	10	6	52	43
5	*n*-$Bu_4N^+HSO_4^-$	0.01	25	1	100	96
6	*n*-$Bu_4N^+HSO_4^-$	0.01	10	3	100	96
7	*n*-$Bu_4N^+HSO_4^-$	0.005	10	3	100	96

a) 6.8 g (22.8 mmol) of **5** was used.
b) Yields were based on **5**.

Experimental

^1H NMR (300 MHz) spectra were recorded on Varian UNITY 300 spectrometer in $CDCl_3$ solutions, using tetramethylsilane as an internal standard. IR spectra were recorded on JASCO IR-810 spectrophotometer. High resolution mass



2 **5** **1**

92% from **2**

a) 1.0 eq. Br_2, 0.0001 eq. AIBN, 50-60°C, 1h
b) 1.5 eq. Br_2, 0.0025 eq. I_2, 70°C, 2h
c) 25% $NaHSO_3$ aq., 40°C, 0.5h
d) 25% NaOH aq., 0.005 eq. $n\text{-}Bu_4N^+HSO_4^-$, 70°C, 2h

Scheme 2

spectrum was obtained with Hitachi M2000A mass spectrometer. Melting point was uncorrected. Solvents and materials were industrial grade and used without further purification. Reactions and purities were checked by Shimadzu GC-14B gas chromatography (column: SE-30 10%, 4.0 mm x 2.0 m; detector: FID; carrier gas: N_2).

3-Chloro-α,β-dibromoethylbenzene (5).

Br_2 (568 g, 3.56 mol) was added dropwise to **2** (500 g, 3.56 mol) in the presence of 2,2'-azobis(isobutyronitrile) (60 mg, 0.356 mmol) at 50-60°C for 1.0 hr. To the resulting mixture was added I_2 (2.3 g, 8.9 mmol) and Br_2 (852 g, 5.33 mol) and the reaction mixture was heated at 70°C for 2 hr. After cooling to 40°C, 25% aqueous $NaHSO_3$ (740 g, 1.78 mol) was added and stirring for 0.5 hr to reduce the excess of Br_2. The lower organic layer was separated to afford crude **5** (1150 g, purity 88%, 3.39 mol, 95% from **2**). The small portion of crude **5** was recrystallized from acetone-H_2O. Colorless crystals; mp 40-41°C; IR (KBr) 1568, 1470, 1440, 1195, 785, 687, 596 cm^{-1}; ^1H NMR $\delta = 3.96$ (1H, dd, $J = 10.5$ and

10.8 Hz), 4.06 (1H, dd, J = 5.4 and 10.5 Hz), 5.07 (1H, dd, J = 5.4 and 10.8 Hz), 7.26-7.32 (3H, m), 7.40 (1H, s).

Found: C, 32.49; H, 2.34; Cl, 11.69. Calcd for $C_8H_7Br_2Cl$; C, 32.20; H, 2.36; Cl, 11.88.

3-Chloro-α-bromostyrene (1).

n-$Bu_4N^+HSO_4^-$ (39 mg, 0.114 mmol) and 10% aqueous NaOH (18.2 g, 45.6 mmol) were added to **5** (6.8 g, 22.8 mmol). The resulting mixture was heated at 70°C for 3 hr. After cooling to rt, the reaction was extracted with toluene and washed with water and brine. The solvent was removed under reduced pressure to afford crude **1** (5.4 g, purity 88% by GC, 21.9 mol, 96% from **5**). The small portion of crude **1** was purified by distillation to give pure **1** boiling at 110-115°C / 0.5 mmHg. Yellow oil; IR (neat) 1562, 1475, 1408, 1212, 882, 782, 700 cm^{-1}; ^1H NMR δ = 5.82 (1H, d, J = 2.1 Hz), 6.14 (1H, d, J = 2.1 Hz), 7.25-7.33 (2H, m), 7.45-7.49 (1H, m), 7.58 (1H, s). HRMS: Found: m / z 215.9322. Calcd for C_8H_6BrCl: M, 215.9340.

One-pot Preparation of 3-Chloro-α-bromostyrene (1).

Br_2 (114 g, 0.711 mol) was added dropwise to **2** (100 g, 0.711 mol) in the presence of 2,2'-azobis(isobutyronitrile) (12 mg, 0.071 mmol) at 50-60°C for 1.0 hr. To the resulting mixture was added I_2 (0.45 g, 1.8 mmol) and Br_2 (171 g, 1.07 mol) and the reaction mixture was heated at 70°C for 2 hr. After cooling to 40°C, 25% aqueous $NaHSO_3$ (148 g, 0.356 mol) was added to reduce the excess of Br_2. The solution was stirred for 0.5 hr, and then n-$Bu_4N^+HSO_4^-$ (1.2 g, 3.6 mmol) and

25% aqueous NaOH (227 g, 1.42 mol) were added to this solution. The resulting mixture was heated at 70°C for 2 hr. After cooling to rt, the reaction was extracted with toluene and washed with water and brine. The solvent was removed under reduced pressure to afford crude **1** (172 g, purity 83% by GC, 0.658 mol, 92% from **2**).

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