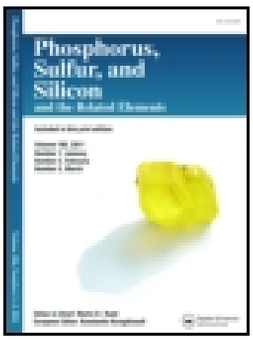

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A Convenient Method for Reduction Dehalogenation of α-Halocarbonyl Compounds Using Benzenethiol in K^+/CH_3CN System

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Abstract

Benzenethiol, as a reductive agent for the dehalogenation of various α-halocarbonyl compounds, is investigated in the K^+/CH_3CN system. The reaction affords the reduced compounds in high yields under mild reaction conditions, especially α-chlorocarbonyl compounds. Furthermore, the reaction performed under ultrasonic irradiation greatly shortens the reaction time.

Keywords

Benzenethiol**;** α-halocarbonyl**;** dehalogenation; K^+/CH_3CN

INTRODUCTION

Dehalogenation has important applications in environmental protection, biochemistry and organic synthesis, especially in practical organic synthesis[1]. A number of reagents have been developed for the reductive dehalogenation of α-halocarbonyl compounds, but most of these reagents have disadvantages in some degree, such as the use of expensive or rare catalysts (Al-Hg[2], NaI/Me_3SiCl_3[3], Bi/NH_4HF_2[4], VCl_2[5], $TiCl_3$[6], In[7], NaTeH[8], $Ru(bpy)_3Cl_2$[9]), long reaction time ($Na_2S_2O_4$[10], Pd[11], phosphines[12], PI_3/P_2I_4[13], iodotrimethylsilane[14]), high temperature (Zn/NH_4Cl[15], Zn/AcOH[16], Al/$(NH_4)_2C_2O_4$[17], polypropylene[18]), and poor yields (organotinhydrides[19]), especially for the reduction of α-chlorocarbonyl compounds. It is well known that the ease of reductive hydrodehalogenation of organic halides follows the general order Br > Cl.

In previous studies, we have introduced a convenient method for the aerobic oxidation of thiols to disulfides using K^+/CH_3CN system[20]. As a part of our work on the synthesis of bioactive lead compounds using ultrasonic or microwave methods[21], we have checked that α-haloketones and dihalides could also be reduced by the same system (benzenethiol /K^+/CH_3CN). The system could be used for the reduction of active halides and sulfides under acid or alkaline conditions. The method has been published as patents [22] by us.

RESULTS AND DISCUSSION

We found that, in the K_2CO_3/CH_3CN system, the yields of the reduced products **2** varied with

the reaction time and the amount of thiols used (Table 1). As shown in Table **1**, a mixture of the reductive product **2a** (27 %) and the displacement product **3a** (56 %) was obtained when the mole ratios of **5a** and K_2CO_3 to **1a** were 1.1 and 1.2, respectively. Compound **2a** was obtained in 87 % yield under the same conditions when excess thiol **5a** (2.25 equiv) was used, but the yield of **2a** decreased gradually with the extension of reaction time and afforded only 45 % yield after 6 h. In contrast, the yield of **3a** increased and gave 80 % yield over 24 h. In the K_2CO_3/CH_3CN system, the reduction product **2a** decreased gradually, and the substitution product sulfide **3a** increased, with prolonged reaction time. And **2a** reacted with disulfide **4a** under the same conditions to give the sulfide **3a** in high yields. The compound **1a** was reduced completely when the amount of thiol **5a** was increased further to 3.0 equiv and **2a** was obtained quantitatively. Besides, the yield of **2a** was not affected by the reaction temperature and the H_2O content of the solvent (V_{H2O}/V_{CH3CN} : 0~10 %).

To expand the reaction conditions, the dehalogenation of α-halocarbonyl compound (**1a**) using a series of potassium halides was carried out. The results are shown in Table 2. As shown, the order of the catalytic activity in the reduction was $KI>K_2CO_3>KBr>>KCl\sim KF$. But in the KBr/CH_3CN or KI/CH_3CN system, reduction product **2a** was obtained in good yield without the formation of sulfide **3a**. Especially with the KI/CH_3CN system, the reduction proceeded to give **2a** in a high yield after 20 min without the formation **3a** using thiol **5a** (1 equiv). When the thiol is omitted, the reaction didn't occur. The reaction solution became red-brown rapidly in the

presence of KI, due to the I_2 generated in the reaction. The reaction solution changed into blue when starch was added. It is likely that the Cl_2 produced reacted with KI to form I_2 and KCl, which promoted the reaction process. However, in the case of KF and KCl, the reaction proceeded very slowly, and it just afforded a small amount of sulfide **3a,** not the reduction product, after 6 h. The reaction solution was strongly acidic as checked by pH test paper. We considered that the acidic medium, derived from Cl_2 produced by the reaction, hindered the process of reduction. In fact, halide **1a** was reduced quickly when one equivalent triethylamine was added. And 2-bromoacetophenone **1j** could be debrominated in the presence of KBr to afford the corresponding ketones in high yields too (entry11, Table 3). The results showed that bromoacetonitrile detected by GC/MS. Based on these results, the reaction mechanism as shown in Scheme 1 was proposed.

We applied the K^+/CH_3CN system with *p*-tolylthiol (**5a**) for the reduction of various *a*-halo substituted compounds to get dehalogenated products (Table **3**). The results indicated that, 1) dehalogenated products **2** were obtained in good to excellent yields in the K^+/CH_3CN system; 2) The reduction of the chlorinated compounds were found to be slower in comparison with those of the brominated compounds (Table 3, entries 8 and 9); 3) Ultrasonic-assisted organic reactions have been applied to a wide range of reaction types, the use of ultrasonic irradiation instead of traditional reducing condition could cut down the reaction time of α-halocarbonyl compound by about 60~80% (Table 3, entries 1 and 9); 4) We tried to treat 2,2-dichloroacetophenone **1j** by

using KI and *p*-tolylthiol in acetonitrile under ultrasonic irradiation for 15h, then dehalogenated acetophenone **2j** was obtained in good yield.

It is well known that preparation of alkanes by the reduction of sulfides is a common methodology in organic synthesis [23]. As shown in Scheme 2, in the K_2CO_3/CH_3CN system, sulfide **3a** (1mmol) was reduced completely with thiol **5a** (1.2mmol) to afford **2a** and disulfide **4a** in a good yield within 20 min. However, **3a** appeared again and increased with the extension of reaction time, and the mixture of **2a**, **3a**, and **4a** was obtained in the end. In the KF, KCl or KBr/CH_3CN system, treatment of **3a** with **5a** also afforded **2a** and **4a** in a good yield, without the formation **3a.** For example, **2a** was obtained in 99% yield in the presence of KBr. Especially the catalytic activity of KF is similar with that of K_2CO_3 in the process, and the reaction catalyzed by KF was completed within 30 min. But about 24 h was required in the KCl or KBr/CH_3CN system. In the presence of KI, no reaction product was formed under the same conditions, owing to the acidity of KI.

CONCLUSION

In conclusion, we showed that the reductive dehalogenation of α-halocarbonyl compounds with benzenethiol as a reductive agent in the K^+/CH_3CN system. The present procedure is attractive of its simple reaction conditions, easy product isolation, low cost, high yields and because the reaction can also proceed under acid or alkaline conditions.

EXPERIMENTAL

Materials and Methods

Melting points were conducted on a Yanaco MP-500 micro meltingpoint apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ as solvent on Bruker AC-300 and Bruker AC-400 instrument using TMS as an internal standard. Elemental analysis was performed on a Yanaco CHN Corder MF-3 automatic elemental analyzer. GC analyses of the compounds were performed on an Agilent Technologies 6890 N Network GC System (with a TCZWAX capillary 30m column).

Synthesis

The *a*-halocarbony1 compound was prepared according to the literature[24]. To a solution of 3-oxo-N,3-disubstitutedpropanamide(0.0722mol) in toluene (80 mL), was added sulfuryl dichloride(0.0722mol) at 20 ^{o}C, then the mixture was stirred for 4h. After the reaction is completed, the solvent was moved and the solid was recrystallized in PE/EA(v/v =1:1).

A mixture of *a*-halocarbony1 compound (1.0 mmol), thiol (2.25 mmol), potassium salt (1.2 mmol) in acetonitrile (5 mL) was stirred at room temperature and in the open atmosphere in a glass reactor. The completion of reaction was monitored by TLC. The reaction mixture was filtered, and evaporation of the filtrate under reduced pressure followed by preparative thin layer chromatography on silica gel afforded the pure products. Among them, compounds **2b** and **2c** are new.

3-Oxo-N-phenylbutanamide 2a: 1H NMR (DMSO-d_6, 400 MHz), δ: 10.08 (s, 1H), 7.57 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.36-7.24 (m, 2H), 7.10-6.97 (m, 1H), 3.54 (s, 2H), 2.20 (s, 3H).

***N*-phenyl-2-(1,2,3-thiadiazol-4-yl)acetamide 2b**: White solid，yield 98%，m.p. 126-128℃; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 4.290 (s, 2H, CH_2), 7.097-7.536 (m, 5H, Ph), 8.340 (br, 1H, NH), 8.594 (s, 1H, thiadiazole-H); Elem. Anal. for $C_{10}H_9N_3OS$: calculated: C, 54.78; H, 4.14; N, 19.16. found:C, 54.60; H, 4.15; N, 19.29.

1-morpholino-2-(1,2,3-thiadiazol-4-yl)ethan-1-one 2c: White solid， yield 77%, m.p. 126-128℃; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 3.671-3.721 (m, 8H, morpholine-H), 4.296 (s, 2H, CH_2), 8.592 (s, 1H, thiadiazole-H); Elem. Anal. for $C_8H_{11}N_3OS$ calculated: C, 45.06; H, 5.20; N, 19.70. found:C, 45.17; H, 4.98; N, 19.93.

1-Piperidin-1-yl-butane-1,3-dione 2d: Yellow liquid, ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 1.47-1.55 (m, 4H), 1.55-1.64 (m, 2H), 1.90 (s, 0.37H), 2.22 (s, 2.52H), 3.30 (t, J = 4.2 Hz, 2H), 3.36-3.58 (m, 4H), 5.11 (s, 0.12H), 14.7 (s, 0.10H).

N-methyl-3-oxobutanamide 2e: ^{1}H NMR (DMSO-d_6, 300 MHz) , δ: 7.5 (s, 1H, NH), 2.25 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 3.66 (s, 2H, CH_2).

1-Morpholinobutane-1,3-dione 2f: pale yellow oil, ^{1}H NMR ($CDCl_3$, 400 MHz) , δ: 2.24 (s, 3H), 3.38 (t, J = 4.8 Hz, 2H), 3.53 (s, 2H) 3.58-3.60 (m, 2H) , 3.62-3.65 (m, 4H).

Acetophenone 2g: ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.60 (s, 3 H), 7.44-7.48 (m, 2 H),7.54-7.58 (m, 1H), 7.95 (d, 2 H, J = 8.2 Hz).

Acetophenone 2h: ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.60 (s, 3 H), 7.44-7.48 (m, 2 H),7.54-7.58 (m, 1H), 7.95 (d, 2 H, J = 8.2 Hz).

Ethyl phenylacetate 2i: ^{1}H NMR ($CDCl_3$, 400 MHz) , δ: 7.40-7.25 (m, 5H), 4.17 (q, J = 8.0 Hz, 2H), 3.63 (s, 2H), 1.27 (t, *J* = 8.0 Hz, 3H).

Acetophenone 2j: ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.62 (s, 3H), 7.45-7.50 (m, 2H), 7.55-7.59 (m, 1H), 8.03 (d, 2H, *J* = 8.2 Hz).

Characterization data for all the other known compounds is agreement with the literature [25].

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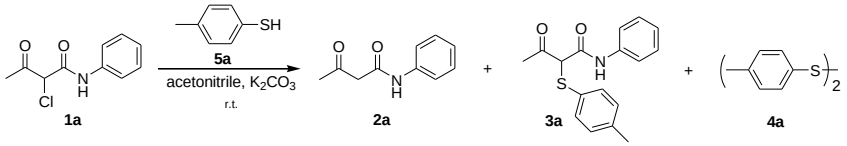
Table 1. Reactions of thiols with active methylene chlorides

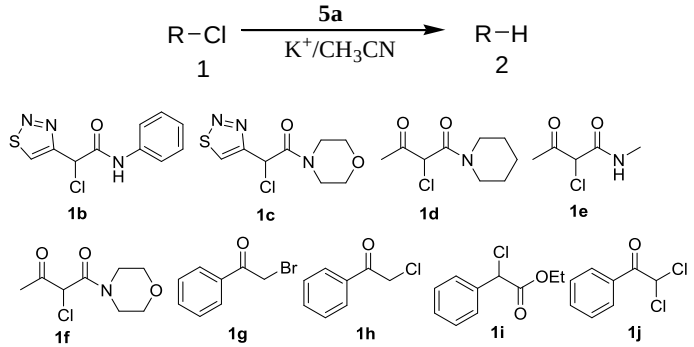


No.	**1a**	**5a**	K_2CO_3	Time	Yiled(%)	
		mmol			**2a**	**3a**
1	1	1.1	1.2	40min	27	56
2	1	2.25	1.2	40min	87	-
3	1	3.0	1.2	1h	~100	-
4	1	2.25	1.2	6h	45	40
5	1	2.25	1.2	24h	-	80

Table 2. Reduction of halides in the K^+/CH_3CN system at room temperature

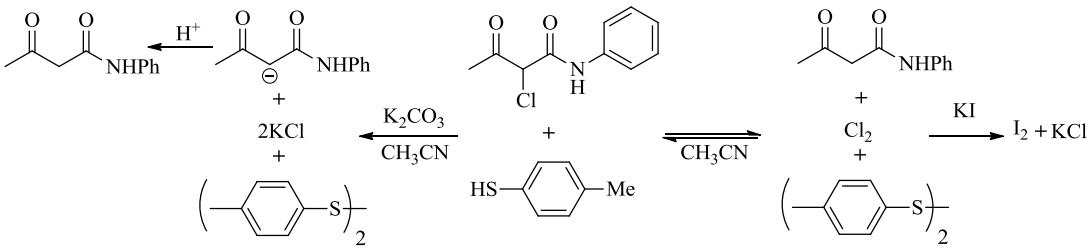
No.	**1a**	**5a**	K^+	Time	**2a** Isolated yield (%)
		mmol			
1	1.0	2.25	KF (1.2)	6h	trace
2	1.0	2.25	KCl (1.2)	6h	trace
3	1.0	2.25	KBr (1.2)	6h	91
4	1.0	2.25	KI (1.2)	20min	82
5	1.0	1.0	KI (1.2)	20min	81
6	1.0	2.25	K_2CO_3 (1.2)	40min	87

Table 3. Dehalogenation of *a*-halocarbony1 compounds (halides) in the K^+/CH_3CN system.

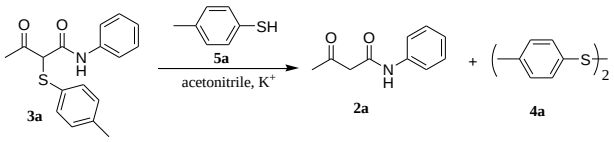


no.	1	5a	K^+	Time	2	Yield (%)[a]
		mmol				
1	**1b**(1.0)	2.25	KI(0.6)	4d (20h[c])	**2b**	98
2	**1c** (1.0)	2.25	K_2CO_3 (1.2)	24h	**2c**	65
3	**1c** (1.0)	3.0	KI(1.2)	24h	**2c**	77
4	**1d**(1.0)	2.25	K_2CO_3 (1.2)	1.5h[b]	**2d**	100
5	**1d**(1.0)	2.25	KBr (1.2)	20h	**2d**	100
6	**1e** (1.0)	2.25	K_2CO_3 (2.4)	45min[b]	**2e**	100
7	**1f**(1.0)	1.2	KI (1.2)	16h	**2f**	70
8	**1g**(1.0)	1.2	KI (1.2)	10min	**2g**	71
9	**1h**(1.0)	1.2	KI (1.2)	7h (3h[c])	**2h**	83
10	**1i**(1.0)	1.2	KI (1.2)	2d	**2i**	87
11	**1j**(1.0)	3.0	KI (3.0)	15h[c]	**2j**	70

[a] Isolated yield [b] by quenching [c]Ultrasound



Scheme 1. The proposed mechanism of the redox reaction in the K^+/CH_3CN system.



Scheme 2. Reduction of sulfides in the K^+/CH_3CN system.