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A Convenient Halogenation Procedure for the Preparation of α-Halocarbonyl Compounds

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Except for substituted acetophenones (p-Y-$C_6H_4COCH_3$, Y=H, Br, CH_3O), simple ketones, β-ketoesters and 1,3-diketones reacted smoothly with a preformed homogeneous mixture of hydrochloric acid and potassium permanganate in acetonitrile to give moderate to good yields of the corresponding α-chlorocarbonyl compounds. Mixtures of α-chloro- and α,α-dichlorocarbonyl compounds were obtained for substituted acetophenones. Brominations proceeded similarly with higher yields when the hydrochloric acid was replaced with hydrobromic acid.

INTRODUCTION

Since α-halocarbonyl compounds are useful synthetic intermediates in a number of widely different organic transformations, numerous methods are available for halogenation of the α-position of carbonyl compounds using various halogenating reagents.[1] These reagents are sometimes troublesome (i.e. Cl_2, Br_2) or unstable.[2] We have been interested for some time in devising some new, more efficient methods for their preparation. In connection with our $KMnO_4$/HX/CH_3CN reagent,[3] we have now developed a convenient halogenation procedure for conversion of carbonyl compounds into α-halo and α,α-dihalocarbonyl compounds. When applicable, the uses of $KMnO_4$/HX/CH_3CN reagents have many advantages, especially when carbonyl compounds can be chlorinated directly with no need of transformation of ketones into enol silyl ether.[4] We describe here a simple and general synthetic procedure for obtaining α-halocarbonyl compounds with $KMnO_4$/HX/CH_3CN reagent in a homogenous one pot reaction. The fascinating features of the halogenation of 1,3-diketones are not only that it is an easily utilizable technique, but it is also a regioselective monohalogenating procedure, resulting in high yields of α-halogenated products where the halogen atom can be chosen by using HCl or HBr.

RESULTS AND DISCUSSION

Chlorination of carbonyl compounds under conventional conditions with various reagents generally leads to polychlorinated α-halocarbonyl compounds,[1] while with our reagent even the simple ketones gave α-monochloro compounds. The products existed as a mixture of ketone and enol forms in a total yield of 56% for cyclohexanone and 2-methylcyclohexanone, respectively. The ratio of enol to ketone was about 3:1 for the case of 2-methylcyclohexanone, while for cyclohexanone the ratio was 1 to 3, as determinated by ^{1}H-NMR using benzene-d_6 as an internal standard. Attempts to increase the yield lead to higher yield of the monochlorinated product, but contamination of the α,α-dichlorinated products is unavoidable.

Chlorination of acetophenones with the $KMnO_4$/HCl/CH_3CN reagent gave mixtures of mono and dichlorinated products. The yield from acetophenone was good (73%), consisting of 58% of the 2-chloro and 15% of the 2,2-dichloroacetophenone. 4′-Bromoacetophenone gave 53% of the 2-chloro-4′-bromoacetophenone and 7% of the 2,2-dichloro-4′-bromoacetophenone. A moderate yield (40%) was obtained from chlorination of 4′-methoxyacetophenone. The product consisted of 24% of the 2-chloro- and 16% of the 2,2-dichloro-4′-methoxyacetophenone. Diethyl malonate was converted to the corresponding α-chloro chlorinated compounds at 60 °C in 86% yield. Ethyl acetoacetate was readily chlorinated at room temperature (ca. 20 °C) with the $KMnO_4$/HCl/CH_3CN reagent to ethyl α-chloroacetoacetate in 80% yield. Similarly 1,3-diketones was chlorinated in α-position without contamination of any dichlorinated product. However, some monochlorinated products existed with their enol forms. Yields for α-chloroacetylacetone, α-chlorobenzoylacetone and α-chlorodibenzoylmethane were 67%, 82%, and 88%, respectively. These results were summarized in Table 1.

A similar condition is applicable for achieving bromination. Typical yields are summarized in Table 2. Bromination of 1,3-diketones (acetylacetone, benzoylacetone, and

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Dedicated to Professor Yu-Shia Cheng on the occasion of her 65th birthday.

Table 1. α-Chlorocarbonyl Compounds Obtained by Using $KMnO_4/HCl/CH_3CN$ Reagent

Entry	Substrate	Product	Yield (%)
1	Cyclohexanone	2-Chlorocyclohexanone	56[a] (1:3)[a]
2	2-Methylcyclohexanone	2-Chloro-6-methylcyclohexanone	56[a] (3:1)[a]
3	Acetophenone	$C_6H_5COCH_2Cl$ $C_6H_5COCHCl_2$	58 15
4	4′-Methoxyacetophenone	p-CH_3O-$C_6H_4COCH_2Cl$ p-CH_3O-$C_6H_4COCHCl_2$	28 16
5	4′-Bromoacetophenone	p-Br-$C_6H_4COCH_2Cl$ p-Br-$C_6H_4COCHCl_2$	54 8
6	Ethyl acetoacetate	$CH_3COCHClCOOCH_2CH_3$	80 (1:2)[b]
7	Diethyl malonate	$(CH_3CH_2O_2C)_2CHCl$	86
8	Ethyl benzoylacetate	$C_6H_5COCHClCOOCH_2CH_3$	82
9	Acetylacetone	$CH_3COCHClCOCH_3$	67 (6:1)[b]
10	Benzoylacetone	$C_6H_5COCHClCOCH_3$	82 (5:1)[b]
11	Dibenzoylmethane	$C_6H_5COCHClCOC_6H_5$	88[c]

[a] Enol/keto ratio determinated by ^{1}H-NMR with benzene-d_6 as internal standard.
[b] Enol/keto ratio determinated by ^{1}H-NMR of isolated product.
[c] Recrystallization with chloroform/hexane (1:7).

dibenzoylmethane) with the $KMnO_4/HBr/CH_3CN$ reagent gave only α-monobrominated products. Yields were good (72%-87%) and the enol forms were always presented (in NMR) in the isolated products wherein the enol forms predominated (Table 2). In the case of dibenzoylmethane, the crude yield was quantitative, and the α-bromodibenzoylmethane was isolated in 87% yield after recrystallization ($CHCl_3$-hexane). Cyclohexanone gave 40% of 2-bromocyclohexanone while the 2-methylcyclohexanone gave a mixture of 2-bromo-6-methylcyclohexanone and its enol form in a ratio of 1 to 3 (41% total yield). Acetophenone, 4′-methoxyacetophenone, and 4′-bromoacetophenone all gave mixtures of mono and dibromocarbonyl compounds with $KMnO_4/HBr/CH_3CN$ reagent. Acetophenone was converted to 2-bromoacetophenone in 60% yield together with 23% of the 2,2-dibromoacetophenone. 4′-Methoxyacetophenone gave 48% of 2-bromo-4′-methoxy-acetophenone and 18% of the 2,2-dibromo-4′-methoxyacetophenone. While 4′-bromoacetophenone gave 2-bromo-4′-bromoacetophenone (73%) along with 9% of 2,2-dibromo-4′-bromoacetophenone. An 87% yield of α-mono brominated diethyl malonates was obtained. The reactions are simple to perform; the required reagents and solvents are economical to use. The only disadvantage of this procedure is that simple ketones sometimes give mixtures of dihalogenated derivatives, but products were easily purified by column chromatography. The reaction of the dibenzoylmethane with $KMnO_4/HI/CH_3CN$ reagent afforded α-iododibenzoylmethane in 95% yield.[5] Since most α-iodocarbonyl compounds are light sensitive and unstable to separate, only an *in situ* generation of α-iodocarbonyl compounds are possible.

CONCLUSION

In summary, a convenient procedure for the preparation of α-halocarbonyl compounds has been developed. This method is complementary to the existing procedures and sometimes could be the method of choice because of its simplicity and higher yield. The results described herein demonstrate regiospecific α-halogenation of 1,3-diketones is possible.

EXPERIMENTAL SECTION

IR spectra (neat or KBr pellet) were run on a JASCO-IR-700 spectrometer. ^{1}H and ^{13}C NMR were recorded on a JEOL-JNM-EX 400 spectrometer; chemical shifts are reported in parts per million downfield from TMS. Mass spectra (EI) were recorded on a Finnigan TSQ-700 mass

Table 2. α-Bromocarbonyl Compounds Obtained by Using $KMnO_4/HBr/CH_3CN$ Reagent

Entry	Substrate	Product	Yield (%)
1	Cyclohexanone	2-Bromocyclohexanone	40[a] (3:1)[a]
2	2-Methylcyclohexanone	2-Bromo-6-methylcyclohexanone	41[a] (4:1)[a]
3	Acetophenone	$C_6H_5COCH_2Br$	60
		$C_6H_5COCHBr_2$	23
4	4′-Methoxyacetophenone	p-CH_3O-$C_6H_4COCH_2Br$	56
		p-CH_3O-$C_6H_4COCHBr_2$	6
5	4′-Bromoacetophenone	p-Br-$C_6H_4COCH_2Br$	73
		p-Br-$C_6H_4COCHBr_2$	9
6	Ethyl acetoacetate	$CH_3COCHBrCOOCH_2CH_3$	81 (2:1)[b]
7	Diethyl malonate	$(CH_3CH_2O_2C)_2CHBr$	87
8	Ethyl benzoylacetate	$C_6H_5COCHBrCOOCH_2CH_3$	88
9	Acetylacetone	$CH_3COCHBrCOCH_3$	72 (1.6:1)[b]
10	Benzoylacetone	$C_6H_5COCHBrCOCH_3$	74 (1:2)[b]
11	Dibenzoylmethane	$C_6H_5COCHBrCOC_6H_5$	87[c]

[a] Enol/keto ratio determinated by ^1H-NMR with benzene-d_6 as internal standard.

[b] Enol/keto ratio determinated by ^1H-NMR of isolated product.

[c] Recrystallization with chloroform/hexane (1:7).

spectrometer, operating at an ionizing voltage of 70 eV. Melting points were recorded on a Mel-temp. instrument and were uncorrected.

$KMnO_4$, HBr and HCl (E. Merck, analytical grade) were used without purification. Starting martials (Aldrich, reagent grade) were purified by distillation or recrystallization before use.

General Procedure for the Preparation of α-Chlorocarbonyl Compounds

$KMnO_4$ (0.474 g, 3 mmol) and CH_3CN (100 mL) were mixed in a round-bottomed flask under magnetic stirring, followed by addition of HCl (37%, 3.8 mL, 45 mmol) and stirred for 5 min. After addition of the substrate (10 mmol) stirring was continued at 60 °C until the solution turned colorless. 1,3-Diketones were chlorinated at room temperature (ca. 20 °C). The progress of reaction was monitored by TLC (silica gel, $CHCl_3$ as eluent). After the solvent was removed under vacuum, $CHCl_3$ (40 mL) was added to the mixture, and the colloidal salts were filtered. After evaporation of the filtrate, separation of products was achieved by passing through a column of silica gel (2.5 cm × 25 cm, E. Merck 70-230 mesh) using $CHCl_3$/hexane (1:1) as eluents to give the pure products.

General Procedure for the Preparation of α-Bromocarbonyl Compounds

The bromination of the corresponding carbonyl compounds (10 mmol) was carried out similarly to that described for the preparation of α-chlorocarbonyl compounds, except that the $KMnO_4$ (0.632 g, 4 mmol) in 100 mL CH_3CN and HBr (47%, 6.8 mL, 60 mmol) were used.

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Key Words

α-Chlorocarbonyl compounds; α-Bromocarbonyl compounds; Potassium permanganate; Chlorination; Bromination.

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5. The Iodination of the dibenzoylmethane (10 mmol) was carried out similarly to that described for the preparation of α-chlorocarbonyl compounds, except that the $KMnO_4$ (0.632 g, 4 mmol) in 100 mL CH_3CN and HI (47%, 6.8 mL, 60 mmol) were used.