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Potassium iodide catalyzed reductive dehalogenation of α-halo-ketones using Hantzsch ester diethyl 1, 4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate as reductant

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Abstract

In the presence of diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (DHP) and a catalytic amount of potassium iodide, several α-halo ketones were easily reduced to the corresponding ketones in acetone media. The procedure presented here showed several merits such as short reaction time, practical experimental and isolated procedure, and excellent yields of products.

Keywords: Dehalogenation; α-Halo ketones; Hantzsch ester; 1,4-Dihydro-2,6-dimethylpyridine-3,5-dicarboxylate; Potassium iodide

The reduced form of nicotinamide adenine dinucleotide coenzyme [NAD(P)H] plays a crucial role in biological systems as a source of two electrons and a proton [1]. Over the past years, a number of 1,4-dihydropyridine derivatives, including the Hantzsch ester, diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate (DHP), have been widely used as models of NAD(P)H to mimic the reduction of various unsaturated compounds [2].

As a mild reducing reagent, the use of DHP in organic reactions is of considerable interest. Studies on the reductions of unsaturated substrates such as ketones, aldehydes [3] and alkenes [4] have been attracted much attention from organic chemists. Additionally, using DHP as the reductant in the reductive amination of aldehydes [5], α,β-unsaturated ketones [6] and multicomponent reaction [7] have been documented as well. Nevertheless, quite a few reports have been published concerning to the dehalogenation of α-haloketones [8,9]. To the best of our knowledge, the use of DHP as reductant for reductive dehalogenation has also not been reported.

Reductive dehalogenation of α-haloketones is one of the important reactions used in organic synthesis [10]. A great number of methods have been introduced for this dehalogenation, such as using organometallic ionic liquid [bmim][$Co(CO)_4$] [11], palladium [12] as a catalyst, *etc*. However, many reported methods suffered from some limitations such as lower yielding, longer reaction time, or using heavy metal as catalysts. As a continuation of our research work in biomimetic synthesis, we wish to report an efficient and practical methodology for the reductive dehalogenation of α-halo ketones in the presence of DHP under mild reaction conditions (Scheme 1).

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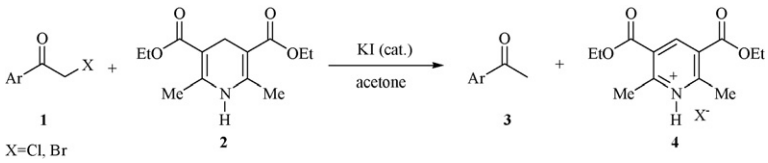


Scheme 1. Reductive dehalogenation using DHP as reductant in the presence of KI.

1. Experimental

Melting points were measured on an electrothemal X6 microscopy digital melting point apparatus. GC–MS spectra were taken on Thermo Finnigan Trace GC–MS. ^{1}H NMR spectra were performed with a 300 MHz Bruker Advance instrument using $CDCl_3$ as a solvent and TMS as an internal standard. The chemicals were obtained from commercial sources and used as received. DHP was prepared according to the procedure reported in literature [18].

α-Halo ketone **1** (3.0 mmol), DHP **2** (3.0 mmol), and KI (20 mol%) were added to acetone (10 mL) in a round-bottomed flask, then the mixture was stirred at room temperature for 3 h. After the reaction was completed (monitored by TLC), the mixture was concentrated under reduced pressure to remove the solvent, 5 mL dilute HCl was added and than the mixture was extracted with diethyl ether (5× 8 mL). The organic phases were combined, washed with dilute hydrochloric acid (5× 5 mL), followed with $NaHSO_3$ solution and water. The solvent was dried over anhydrous Na_2SO_4 and then concentrated on a rotary evaporator to obtain the desired product **3**, which was further purified by preparative TLC. All compounds were characterized by MS or ^{1}H NMR and compared with the authentic samples.

2. Results and discussion

Initially, we investigated the reactive dehalogenation of 2-bromo-4′-nitroacetophenone in the presence of DHP in ethanol solvent at ambient temperature. It was found that the reductive dehalogenation reaction took a long time and many side products were accompanied. It is well known that the halogen-exchange reaction proceed smoothly in acetone, so we tried the reaction using potassium iodide as an additive to promote the reductive reaction in several solvents. The results are listed in Table 1. As can be seen from Table 1, acetone is best choice among the screened solvents, the reaction afford the product 4-nitroacetophenone in the presence of potassium iodide with 84% yield in 5 h (entry 1, Table 1).

Encouraged by this result, we further demonstrated the influence of the amount of iodides of the present method by the reaction of 2-bromo-4′-nitroacetophenone reacted with DHP under the above unoptimum conditions (Table 2), the reaction could not be occurred in the absence of the iodide, which indicated that the iodide plays a crucial role in the process of the reaction (Table 2, entry 1). When the 5 mol% amount of the KI was used, the yield of the product reached up to 83% at ambient temperature for 8 h. Increasing the amount of KI from 5 to 50 mol%, the reaction yields ranged between 83% and 85%, respectively. Therefore, 20 mol% of KI was enough much to push the reaction forward to complete. NaI was also found to be an effect additive in this reaction with slightly prolong reaction time and lower yields (Table 2, entries 8–11).

Then, the scope and the generality of the present method were further demonstrated by the reaction of various α-halo ketones **1** with DHP **2** on the basis of the optimized reaction conditions mentioned above. The results are listed in

Table 1
Effects of solvents on reductive dehalogenation reaction.

Entry	Solvents	Time (h)	Yield (%)[a]
1	CH_3COCH_3	5	84 (>90)[b]
2	CH_3CH_2OH	8	38
3	CH_3CH_2OH (95%, v/v)	8	51
4	CH_3OH	8	20
5	$CHCl_3$	24	Trace
6	$C_6H_5CH_3$	24	–

[a] Isolated yield.
[b] GC yield.

Table 2
Influence of the amount of catalysts on reductive dehalogenation.

Entry	Amount of catalyst (mol%)	Time (h)	Yield (%)[a]
1	None	24	Trace
2	KI 5	8	83
3	KI 10	5	84
4	KI 15	3.5	82
5	KI 20	3	85
6	KI 25	3	81
7	KI 50	4	80
8	NaI 10	8	80
9	NaI 15	6	81
10	NaI 20	4	82
11	NaI 25	4	80

[a] Isolated yield.

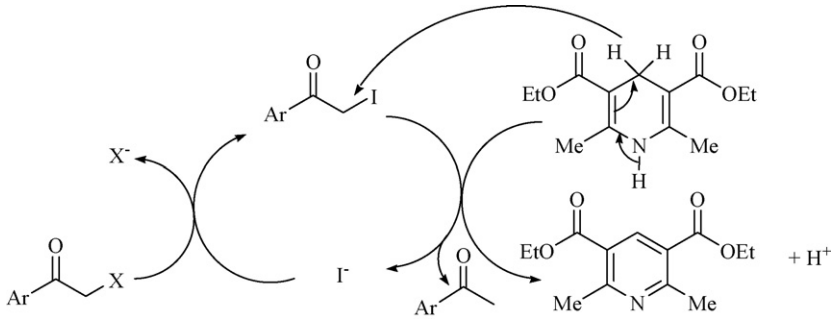
Table 3
The reductive dehalogenation reaction catalyzed by KI using DHP as reductant.

Entry	α-Halo ketones **1**	Time (h)	Products **3**	Yield (%)[a]	m.p. (°C)	lit. m.p. (°C)
1	2-Bromo-4′-nitrophenylethanone **1a**	3	**3a**	85	79–81	79–80 [13]
2	2,4′-Dibromophenylethanone **1b**	1.25	**3b**	88	49–51	49–50 [14]
3	2-Bromo-4′-chlorophenylethanone **1c**	2	**3c**	85	Liquid	15–17 [15]
4	2-Bromoacetophenone **1d**	1.75	**3d**	83	Liquid	15–17 [15]
5	2-Bromo-4′-methoxyphenylethanone **1e**	2.25	**3e**	83	Liquid	30–36 [16]
6	2,4′-Dichlorophenylethanone **1f**	8	**3c**	86	Liquid	15–17 [15]

[a] Isolated yield.

Table 3. As illustrated in Table 3, electronic effects and the nature of substituents on the aromatic ring did show certain effects in terms of reaction time under the reaction conditions mentioned above. When aromatic ring containing electron-withdrawing groups (such as nitro group, halide) were employed (Table 3, entries 1–3), a longer reaction time was required than those of electron-donating groups (such as methoxyl group) (Table 3, entry 5). It is also observed that the relatively reactive aryl bromides showed better results in all case than the chloride with higher yields and shorter reaction time. It is also worthy of note that the substituted functional groups of NO_2 on aromatic ring were tolerant towards this reductive system conditions (Table 3, entry 1).

According to the reported mechanisms concerned about the transfers of hydrogen from NAD(P)H or its model compounds [17] to substrates, we proposed a plausible hydrogen-transfer mechanism for this conversion involved in the halogen-exchange reaction of α-halo ketone with I^- (Scheme 2). First, α-halo ketone react with I^- to give the α-iodoacetophenone due to the I^- serves as both a good nucleophile and a good leaving group. Then, on the next step, α-iodoacetophenone was deiodinated by DHP to afford corresponding ketone and I^-. The produced I^- could directly go into the next catalytic cycle.



Scheme 2. Proposed hydrogen-transfer mechanism for the reductive dehalogenation of α-halo ketones by DHP.

3. Conclusions

We have developed a practical, efficient and convenient dehalogenation procedure for converting α-halo ketones to corresponding ketones by using DHP as reductant. This procedure offers several advantages such as short reaction time, simple experimental and isolated procedure, satisfactory yields of products. Further application of the catalytic system to other hydrogen-transfer is on progress.

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