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HI gas as a reagent for α-alkylation reaction with two ketone molecules

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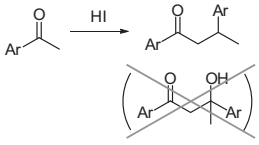
ABSTRACT

To develop the utilization of HI as an 'old but new' reagent, we found that the reaction of acetophenone analogues with HI gas proceeded to give an α-alkylated product, which is derived from the two ketone molecules. It was possible to conduct the reaction in solvent-free and various organic solvents under anhydrous conditions. From the investigation on the reaction mechanism, we proposed that HI acts as an acid and a reducing agent.

In the past decades, numerous numbers of reagents have been reported for organic synthesis. Not only newly developed reagents, but also reagents known well for many years to have potential as a novel synthetic reagent. Acidic reagents are one of the important types, and it is known that their acidity is critically dependent on moisture. Hydrogen iodide (HI) is utilized for organic synthesis as an acid,[1–3] reducing agent,[4–6] nucleophile,[2,7] and so on.[8] HI is commercially available as a 55–57 wt % aqueous solution for use as a synthetic reagent. But, in some reactions, anhydrous conditions are necessary to sustain the reaction. There are various methods for forming anhydrous HI, such as the combination of tetrahydronaphthalene and I_2,[9] RSH and I_2,[10] ROH and I_2,[11] RCOOH and I_2,[12] etc.[13] They are useful in a laboratory-scale experiment, but always form unnecessary by-products. Within the industrial sector, anhydrous HI can be utilized for dry etching ITO films.[14] It can also be used in a gaseous state. In order to utilize anhydrous HI gas for organic synthesis as an 'old but new' reagent, we herein report a novel α-alkylation of acetophenone derivatives with HI, along with the finding that HI acts as both an acidic and a reducing reagent in that reaction.



HI is noncorrosive to many metals under moistureless conditions. Therefore, stainless steel, latex tubes, and glassware can be used as an apparatus. To get anhydrous HI gas for the experiment, we constructed the system depicted in Figure 1. It consisted of an HI cylinder, argon cylinder (to exclude moisture in apparatus), stainless tube, Tygon® tube, control valve, flow meter (to visualize a flow of gas), rubber septum (to pick up HI gas with a disposable syringe), buffer pot (to prevent backflow into line system), and a pot with aqueous NaOH (to neutralize HI gas). (*Caution*!: HI is corrosive when in contact with moisture. The experiment should be conducted with a fume hood.) The tube line was exchangeable with a vacuum pump. Before filling the apparatus with HI gas, the stainless tube is dehydrated by heating with a heat gun in vacuo, and then filled with argon gas. HI gas was taken up through a rubber septum with a syringe attached with a disposable needle, and was then immersed into a reaction vessel to cause a small decompression. The reaction vessel is useable as ordinary glassware. And nitrogen gas was introduced into the vessel to release the difference in pressure against the atmosphere. After all of the reagent was introduced, the reaction was conducted under sealed conditions.

As is expected with an acidic reaction, we examined the reaction of acetophenone with HI gas to promote the aldol reaction. To our surprise, α-alkylated product, 1,3-diphenylbutan-1-one, was obtained at a yield of 61% when 1 equiv of HI was treated with acetophenone at 25 °C for 1 d under solvent-free conditions (Table 1, entry 1). The product consisted of two acetophenone

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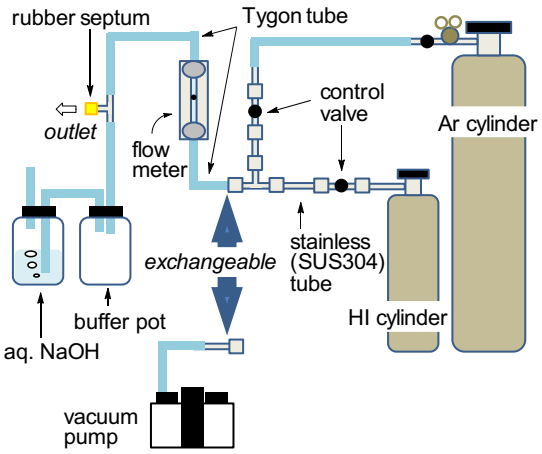


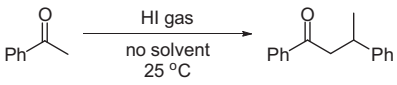
Figure 1. Experimental system to take up anhydrous HI gas.

molecules. Incrementing the amount of HI was inefficient (entries 2 and 3), whereas prolonging the reaction time was slightly effective at increasing the yield, in spite of the remaining initial acetophenone (entries 4 and 5). This reaction was inhibited by using an aqueous solution of HI even in refluxing conditions (entry 6), although toluene and $CHCl_3$ could be utilized as a solvent (entries 7 and 8). Therefore, anhydrous conditions are important to sustain this reaction. The reaction with 1,4-dioxane decreased the reaction rate (entry 9). Thus, the solvent having a lone pair acting as a Brønsted base is inefficient in this reaction because the coordination of protons at that lone pair serves to decrease the reactivity.

To give information on the scope and limitations, various ketones were treated with HI gas (Table 2). As a result, some ketones could be applied to this α-alkylation. Halogen and alkyl substituent on a phenyl ring in acetophenone preserved the reaction progress even in decreasing the yield (entries 1–5). However, the reaction of compounds bearing the hydroxy, naphthyl, and heteroaromatic group did not sustain a reaction (entries 6–10). Alkyl ketone, *tert*-butyl methyl ketone, and cyclohexyl methyl ketone, could not also give the corresponding products (entry 11 and 12). Additional substituent on the methyl group of acetophenone leads to the disadvantageous result of the corresponding α-alkylation product (entry 13).

We focused on the mechanism of this unique reaction, although limitations to this reaction do exist. We could not isolate the apparent by-products in those reactions. Thus, we tried to react the plausible by-products with HI gas. At first, we examined the possibility of the dehydroxylation of aldol product because the reduction of benzyl alcohol by HI was reported in several Letters.[6a,b,d] The reaction of the aldol product of acetophenone, 3-hydroxy-1,3-diphenylbutan-1-one,[15] with HI gas for 2 h under the same conditions mentioned above gave the α-alkylation product in 56% yield accompanied by the formation of acetophenone. However, when the reaction was conducted for 10 min, the formation of acetophenone (43%)[16] and the α-alkylated product (12%) was observed. Results resembled those in the reaction of acetophenone with HI gas for 10 min (Scheme 1). The equilibrium of the aldol reaction would lean to acetophenone under these reaction conditions. And the retro-aldol reaction of 3-hydroxy-1,3-diphenylbutan-1-one was easily occurred to give acetophenone, followed by the formation of the α-alkylated product. Therefore, the aldol product would not be able to exist as a stable intermediate in this reaction. Next, we examined the reaction of the

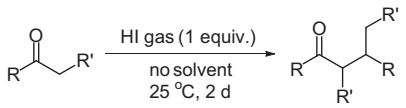
Table 1
Reaction of acetophenone with HI[a]



Entry	Equiv of HI	Time (d)	Yield[b,c] (%)
1	1	1	61 [27]
2	2	1	42 [18]
3	4	1	45 [14]
4	1	2	69 [24]
5	1	3	62 [18]
6[d]	1	2	9 [45]
7[e]	1	2	68 [11]
8[f]	1	2	69 [5]
9[g]	1	2	27 [65]

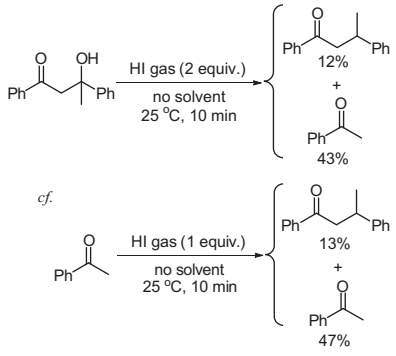
[a] The reaction was conducted with 1 mmol of acetophenone.
[b] Determined by integration of ^{1}H NMR using *p*-chlorobenzaldehyde as an internal standard.
[c] Value in parenthesis is % yield of recovered starting ketone.
[d] 55 wt % aq HI was used.
[e] Toluene was used as a solvent (concentration: 3.3 M).
[f] $CHCl_3$ was used as a solvent (concentration: 3.3 M).
[g] 1,4-Dioxane was used as a solvent (concentration: 3.3 M).

Table 2
Reaction of various ketones with HI gas[a]



Entry	R	R′	Yield[b,c] (%)
1	*p*-F-C_6H_4	H	29 [42]
2	*p*-Cl-C_6H_4	H	31 [48]
3	*p*-Me-C_6H_4	H	47 [42]
4	*m*-Me-C_6H_4	H	46 [41]
5	*o*-Me-C_6H_4	H	48 [12]
6	*p*-HO-C_6H_4	H	N. R.[d]
7	1-Naphthyl	H	N. R.[d]
8	2-Naphthyl	H	N. R.[d]
9	3-Pyridyl	H	N. R.[d]
10	3-Thenyl	H	N. R.[d]
11	*t*-Bu	H	N. R.[d]
12	Cyclohexyl	H	N. R.[d]
13	Ph	Me	0 [60]

[a] The reaction was conducted with 1 mmol of ketones.
[b] Determined by integration of ^{1}H NMR using *p*-chlorobenzaldehyde as an internal standard.
[c] Value in parenthesis is % yield of recovered starting ketone.
[d] N. R. = no reaction.



Scheme 1. Reactions of aldol product with HI.

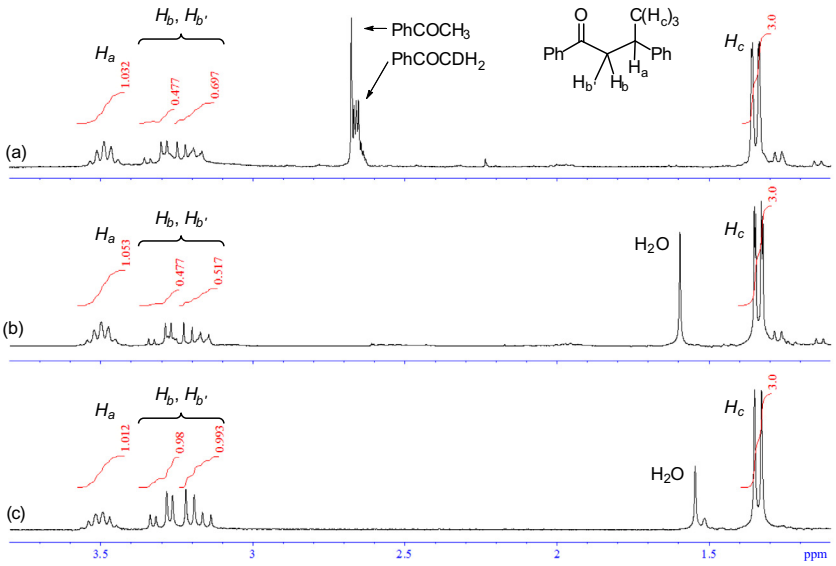
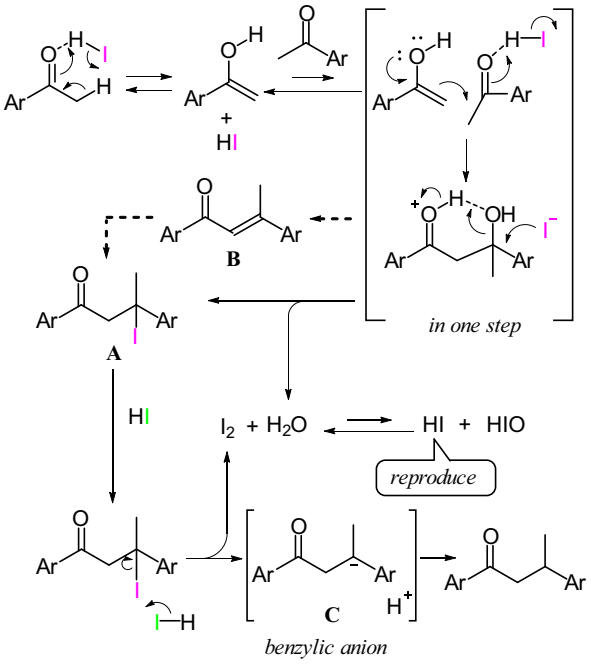


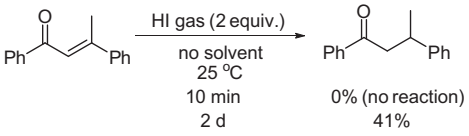
Figure 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of (a) the crude mixture and (b) α-alkylated product after column chromatography obtained by the reaction in toluene-d_8, and (c) α-alkylated product by the reaction under solvent-free conditions. Integral values were determined by the estimation of methyl peaks (H_c) as 3 protons.



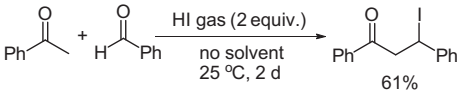
Scheme 2. Plausible reaction mechanism.

compound derived from aldol condensation, 1,3-diphenyl-2-buten-1-one (Eq. 1).[17] However, no products were observed after a period of 10 min, which is a time to give the α-alkylated product in the case of the reaction of the aldol product. Prolonged reaction time gave the α-alkylated product in 41% yield. This result suggested that the reaction through the aldol condensation product is not the main path in the reaction. When the reaction of acetophenone and benzaldehyde was performed under the same conditions, we could obtain the iodinated product, 3-iodo-1,3-diphenylpropan-1-one, in 61% yield (Eq. 2). Thus, 1,3-diaryl-3-iodobutan-1-one is one of plausible intermediates. There is one report about the formation of 3-aryl-3-iodobutan-1-one analogue, 3-iodo-3-(2-acetoxyphenyl)-1-benzoxepin-5(2*H*)-one which was obtained in 13% yield from the reaction of 6a-hydroxy-11a-methylpterocarpan by oxidation with $Pb(OAc)_4$ and I_2.[18] And we could not synthesize 3-iodo-1,3-diphenylbutan-1-one. Therefore, we had to give up the investigation of the reaction with the iodinated compound.

To reveal the possibility of a radical species, we tried trapping radical species using deuterium (Fig. 2). The reaction was conducted in 3.3 M toluene-d_8 under the same conditions represented in entry 7 in Table 1. After the exclusion of HI under reduced pressure, the crude mixture and purified product were measured by ^{1}H NMR in $CDCl_3$ (Fig. 2a and 2b). Focused on the benzylic position, the integration of 1 proton was obtained at H_a (3.51 ppm) with the change of a sextet-like coupling into a quintet-like one. Therefore, the reduction at benzylic position would proceed under a non-radical pathway. As for the results, ca. 50% decrease in the integration of protons at H_b and $H_{b'}$ (3.18 and 3.30 ppm) was observed, accompanied by the contamination of diffused peaks (Fig. 2a and 2b vs 2c). Furthermore, the exchange of deuterium at the α-position of acetophenone was also observed (Fig. 2a). We also found that the deuterium was contaminated at the α-position of the α-alkylated product when it was treated with 2 equiv of HI with toluene-d_8. We were unable to explain the reason for the formation of the deuterated acetophenone. But, considering the formation of the enol radical of acetophenone, the aldol product should be obtained by the addition of the enol radical toward another carbonyl group, followed by H-abstraction by the alkoxy radical.[19] However, the aldol product easily gave the starting acetophenone (Scheme 1). Therefore, a more efficient reaction path for the α-alkylation reaction would be plausible under an ionic pathway compared with a radical one.



(1)



(2)

Robinson et al. reported the reduction of the olefin in 1,2-diphenylpropene with HI.[20] They noted the possibility of the reaction to proceed Markovnikov addition of HI followed by the reduction of benzyl iodide with HI. From these facts, we proposed the reaction mechanism depicted in Scheme 2. Enol formation of acetophenone proceeds by activation with HI working as an acid. An aldol reaction followed by a dehydroxylation reaction mediated by the attack of close iodide would occur to give the iodinated intermediate (A). Proceeding the aldol reaction under acidic conditions, the formation of A was achieved in one-step manner by the activation the hydroxy group with the proton on the carbonyl group directly. The aldol condensation product (B) might be also formed, but that mechanism was a minor path as mentioned above. The reduction of A by HI occurred, accompanied by the formation of I_2. The nucleophilic attack of iodide from HI toward iodine atoms in the intermediate A produced the anion (C), stabilized by benzylic resonance.[21] Finally, the protonation of C gave the desired α-alkylated product. The decrease in the reaction rate of the halogenated compound would be influenced by the retardation of initial enol formation because of the decrease in the protonation ability of carbonyl oxygen via the electron-withdrawing nature of halogen atom (Table 2, entries 1 and 2). The decrease of the yield in the case of the methyl substituted acetophenone could be explained by the lower stability of the benzyl anion (C) (Table 2, entry 3). Thus, this reaction only proceeds smoothly in the case of the good combination of the enol formation and the reduction of benzyl iodide.

Based on the mechanism in Scheme 2, two HI molecules (depicted by purple and green iodines in Scheme 2) are necessitated to give the α-alkylation product. However, 1 equiv of HI is sufficient to give the product in over 50% yield (Table 1, entry 4). Although we could not obtain any critical information to explain this contradiction, we supposed the disproportionation of I_2 and H_2O which are formed in this reaction.[22] The consumption of HI would be achieved to give the product efficiently, although an equilibrium constant of that disproportionation is small.

In summary, we found that, by using anhydrous HI gas, a novel reaction of acetophenone derivatives proceeded to give α-alkylated compounds. This reaction could be applied under solvent-free conditions, and 1 equiv of HI was sufficient to form the product. From the investigation of the reaction mechanism, we proposed that HI participates as both an acid and a reducing agent. And we also showed that HI gas can be handled in a laboratory-scale experiment. Further utilization of HI will be opened from our results and another reaction using HI gas is underway.

Supplementary data

Supplementary data (the detailed reaction procedure, characterization, and NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.071. These data include MOL files and InChiKeys of the most important compounds described in this article.

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