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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.

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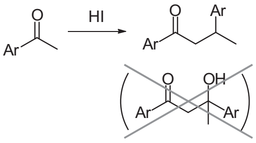
In the past decades, numerous numbers of reagents have been reported for organic synthesis. Not only newly developed reagents, but also reagents known well for many years to have potential as a novel synthetic reagent. Acidic reagents are one of the important types, and it is known that their acidity 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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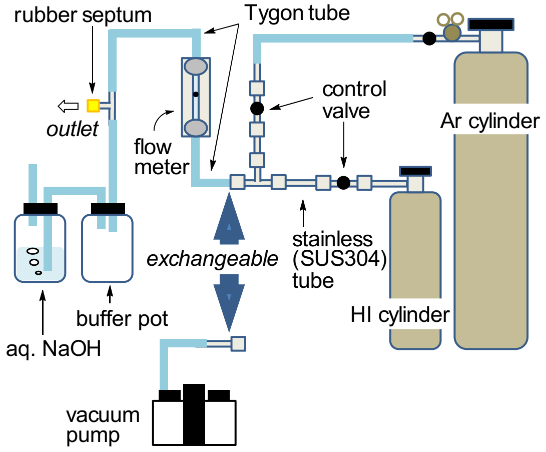
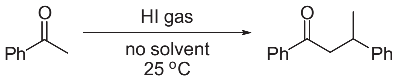


**Figure 1.** Experimental system to take up anhydrous HI gas.

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).

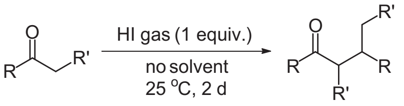
**Table 1**
Reaction of acetophenone with HI[a]



| 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 $^1H$ 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).

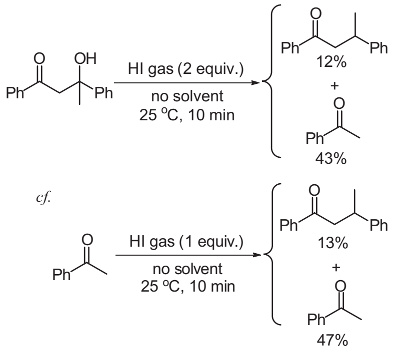
**Table 2**
Reaction of various ketones with HI gas[a]



| 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 $^1H$ NMR using *p*-chlorobenzaldehyde as an internal standard.
[c] Value in parenthesis is % yield of recovered starting ketone.
[d] N. R. = no reaction.

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



**Scheme 1.** Reactions of aldol product with HI.

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